



## Common uterine disorders in the bitch: challenges to diagnosis and treatment

*Distúrbios uterinos comuns em cadelas: desafios no diagnóstico e tratamento*

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### Abstract

Diagnostic tools for common uterine disorders like cystic endometrial hyperplasia (CEH), mucometra, hydrometra or pyometra as well as effective treatments are discussed. Cystic Endometrial Hyperplasia (CEH), a chronic degenerative disease of the endometrium, coincides with delayed uterine clearance of fluids after mating and reduced uterine contractions and perfusion. Since in bitches with CEH, adherence, colonization and growth of bacteria is facilitated, the disease can be complicated by inflammation and infection, which can be diagnosed by uterine swabs or biopsy from the cranial uterine body after transcervical catheterization during oestrus. The diagnosis can furthermore be made by clinical examination, abdominal sonography and a blood picture (total white blood cell count, band neutrophils, percentage of band neutrophils, segmented neutrophils, monocytes and lymphocytes, cholesterol, albumin). Measurement of C reactive protein and prostaglandin(PG)M can help to diagnose beginning sepsis and systemic inflammatory response syndrome (SIRS). Conservative treatment should be restricted to breeding bitches with mild, beginning CEH and regular cycles; furthermore when operation is not possible. The treatment of choice is the repeated administration of the antiprogesterone aglepristone combined with broad spectrum antibiotics. Pyometra is caused by bacteria that belong to the physiological vaginal flora, *Escherichia coli* is mostly involved. Clinical symptoms will be very variable; diagnosis aims to quickly differentiate between beginning CEH/pyometra and advanced pyometra complicated by SIRS and sepsis. The usual diagnostic possibilities like vaginoscopy, cytology, sonographical examination and x-ray can be supplemented by measurement of C reactive protein and PGM, combined with assessment of the percentage of band neutrophils. Only bitches with mild pyometra and no signs of intoxication or SIRS should be conservatively treated. Best results were obtained with the anti-progestin aglepristone, combined with broad spectrum antibiotics and eventually with natural or synthetic prostaglandins (PGF $2\alpha$ ). Resolution of the uterus was achieved in most bitches within 4 weeks. Intravaginal or peroral application of PGE1 is under investigation.

**Keywords:** diagnostic marker, endometrial hyperplasia, infection, pyometra, treatment.

### Resumo

*Ferramentas de diagnóstico para distúrbios uterinos comuns como hiperplasia endometrial cística (CEH), mucometra, hydrometra ou pyometra, além de tratamentos efetivos são discutidos. Hiperplasia endometrial cística (CEH), uma doença degenerativa crônica do endométrio, coincide com a limpeza atrasada dos fluidos uterinos após acasalamento e contrações uterinas reduzidas e perfusão. Como em cadelas com CEH a aderência, colonização e crescimento de bactéria é facilitado, a doença pode ser complicada por inflamação e infecção, que pode ser diagnosticado por amostras uterinas ou biopse do corpo uterino craniano após cauterização transcervical durante o estro. O diagnóstico pode também ser feito por exame clínico, ultrassonografia abdominal e uma imagem do sangue (contagem total de células brancas, faixa de neutrófilos, porcentagem de faixa de neutrófilos, neutrófilos segmentados, monócitos e linfócitos, colesterol, albumina). A medida da proteína reativa C e prostaglantina (PG)M podem ajudar a diagnosticar o início de sepse e síndrome de resposta inflamatória sistêmica (SIRS). O tratamento conservador deve ser restrito a cadelas de reprodução com CEH inicial leve e ciclos regulares, e também quando a operação não é possível. O tratamento escolhido é a administração repetida de antiprogesterona aglepristone combinado com antibióticos de grande espectro. A piometria é causada por bactéria que pertence à flora vaginal fisiológica, e *Escherichia coli* é o mais envolvido. Sintomas clínicos serão muito variáveis, o diagnóstico objetiva a diferenciação rápida entre CEH/piometria inicial e piometria avançada complicada por SIRS e sepse. As possibilidades de diagnóstico usuais como vaginoscopia, citologia, exame sonográfico e raio-x podem ser suplementados por uma medida de proteína reativa C e PGM, combinados com uma avaliação do percentual de faixa de neutrófilos. Apenas cadelas com piometria leve e nenhum sinal de intoxicação ou SIRS devem ser tratadas de forma conservadora. Os melhores resultados foram obtidos com antiprogesterona aglepristone, combinado com antibióticos de grande espectro e eventual com prostaglandinas sintéticas ou naturais (PGF $2\alpha$ ). A resolução do útero foi alcançada na maioria das cadelas em 4 semanas. A aplicação intravaginal ou peroral do PGE1 está sob investigação.*

**Palavras-chave:** hiperplasia endometrial, infecção, marcador de diagnóstico, piometria, tratamento.



## Introduction

Common uterine disorders like cystic endometrial hyperplasia (CEH), mucometra, hydrometra or pyometra are sometimes difficult to diagnose. The symptoms are often unspecific and the degree is variable. Therefore the search for diagnostic markers is ongoing and only recently, some proved to be very useful.

For a long time, ovariohysterectomy was considered the only recommendable treatment against pyometra. During the last decade, new treatments have been scientifically evaluated and can be recommended in defined cases. The present article will give an overview over advanced diagnostic and therapeutical possibilities concerning CEH, mucometra, hydrometra and pyometra.

## Cystic Endometrial Hyperplasia (CEH)

Cystic Endometrial Hyperplasia (CEH) is a chronically developing degenerative disease of the endometrium that is triggered by progesterone (P4) during metestrus. Bacterial infection usually is not present but may occur while the disease progresses and a pyometra may develop (DeBrosschere et al., 2001; Smith, 2006).

### *Pathogenesis*

Typical pathological findings are proliferation of the endometrium and cystic degeneration of the endometrial glands, sometimes combined with increased secretory activity of the glands and accumulation of mucus in the uterine lumen (mucometra, hydrometra). Whilst the disease may begin at an earlier age and proceed slowly, clinical symptoms like fertility disturbances or mucous vaginal fluor are mostly seen in older bitches. The oestrus cycle may still be regular (Egenvall et al., 2001). The pathogenesis of CEH is still not well understood, however, it is widely believed that during the oestrus cycle, the uterus is primed by oestrogens (E2) which triggers proliferation of the endometrium and increases the numbers of the P4 receptors. In bitches with CEH, the consecutive down regulation of E2 receptors may be delayed. Since the uterus is very sensitive during the early luteal stage of the cycle, any uterine irritant may cause hyperplasia of the endometrium and the signs of CEH; however withdrawal of P4 may reverse these symptoms, which proves the importance of P4 for pathogenesis (Nomura et al., 1990; De Bosschere et al., 2002; Chen et al., 2006). Recently, it was found the in bitches with CEH, the uterine clearance of fluids after mating was delayed, because of reduced uterine contractions and perfusion. Short term administration of systemic antibiotics improved these findings (England et al., 2012).

### *Complications*

Complications are inflammation with or without infection; in bitches with CEH, adherence, colonization and growth of bacteria is facilitated (Hagman and Kühn, 2002) which promotes the development of pyometra, a very often life threatening condition (Hardy and Osborne, 1974, Hagman, 2014). In horses it was found that under progesterone the epithelium becomes less permeable to bacteria causing a decrease in leucocyte invasion; furthermore, detoxifying agents usually present in uterine secretions are lacking (Gunnink, 1973).

### *Diagnosis*

Diagnosis is mostly made by history (no disturbance of the general health, fertility disturbance), clinical (eventual mucous vaginal fluor) and sonographical findings. Sonographically, the proliferated endometrium, multiple cysts within the uterine wall and the endometrium sometimes filling the uterine lumen as well as fluids of different amounts within the lumen can be seen. In many cases, ovarian cysts are present. Inflammation and infection can be diagnosed by uterine biopsy from the cranial uterine body after transcervical catheterization during oestrus, however, complications like development of haemomucometra and endometritis have been described (Günzel-Apel et al., 2001). Furthermore cytological and bacteriological evaluation of samples taken by uterine cannulation has been described (Watts and Wright, 1995, Watts et al., 1996, 1998). Even though the sampling was possible during all cycle stages, complications like endometritis and vaginitis were described. The bacteriological swabs taken during pro-oestrus and oestrus were mostly positive for bacteria and these bacteria were the same as detected in the cervix and cranial vagina (Watts et al., 1996). Fontaine et al. (2009) used the same technique for the diagnosis of endometritis in 26 infertile but sonographically normal bitches; 21 of these were examined in diestrus, the others in pro-oestrus and oestrus. The uterus was flushed via the catheter with sterile saline solution and the medium resaspirated and used for cytological and bacteriological evaluation. They found 38% of bitches positive for endometritis, 70% of these were positive for bacteria. Authors state that early anoestrus would be the preferable time for this diagnostic technique, since the uterus is no longer under progesterone and thereby less sensitive for bacterial infection. Sampling during diestrus caused pyometra in two



of 26 bitches (Fontaine et al., 2009). Diagnosis can be substituted by blood analyses, which are helpful to recognize beginning inflammation and infection. The total white blood cell count, band neutrophils, percentage of band neutrophils, segmented neutrophils, monocytes and lymphocytes are higher in pyometra cases (Fransson et al., 1997), the cholesterol concentrations are higher and the albumin levels lower than in CEH cases without infection (Hagman et al., 2006). When the general status of health is decreased, other blood parameters will clearly indicate infection of the uterus: C reactive protein and prostaglandin(PG)M have been described to be useful (see chapter pyometra).

#### *Treatment*

Conservative treatment of CEH is possible, however, only in defined cases. The prognosis is poor in older bitches with advanced CEH (high grade proliferation, endometrial and ovarian cysts) and irregular cycles. Conservative treatment should be restricted to breeding bitches with mild, beginning CEH and regular cycles; furthermore when operation is not possible. The treatment of choice is the s.c. administration of 10 mg/kg aglepristone (Alizine®, Virbac, F), twice within 48 h; further injections after 8 and 15 days, resp., may be necessary which should be decided during sonographical examination of the uterus (Fieni, 2006; for review: Fieni et al., 2014). Fieni (2006) additionally administered prostaglandinF2 $\alpha$  (cloprostenol 1  $\mu$ g/kg s.c.) from day 3 to 7 to accelerate the reduction in uterine lumen diameter in cases of pyometra. They increased the success rate by day 90 from 60 to >80%. The author of this manuscript never used prostaglandins during conservative treatment of CEH. According to England et al. (2012), short term administration of systemic antibiotics improves uterine contractions and perfusion after mating and may improve fertility.

#### *Prognosis*

The prognosis depends on the clinical findings. The disease cannot be healed but the progress slowed down. Prophylactic s.c. application of aglepristone after each oestrus has been discussed. Similar endometrial changings like fibroses with degeneration of endometrial glands and pseudoplacental endometrial hyperplasia, leading to infertility in bitches, can be diagnosed histologically (Mir et al., 2013). Diagnostic measures, treatment and prognosis are the same as in case of CEH.

### **Pyometra**

Pyometra is defined by the presence of haemopurulent or purulent fluids in the metestrus uterus (Dow, 1959).

#### *Pathogenesis*

Pyometra mostly coincides with signs of CEH and is supposed to be a complication of this disease in most cases (De Brosschere et al., 2001, 2002). Pyometra without CEH is seldom but possible and mainly concerns young bitches (Verstegen et al., 2008, own observation). Causative bacteria have been found to belong to the physiological vaginal flora and to derive from the cervix and caudal vagina invading the uterus during pro-oestrus and oestrus (Watts et al., 1996); *Escherichia coli* is mostly involved (Hagman and Kühn, 2002). The early metestrus uterus triggered by oestrogen and sensitized by progesterone together with the accumulation of fluids is supposed to be especially susceptible to bacterial infections (Dow, 1959, Hardy and Osborne, 1974). The bacterial colonization leads to local stimulation of the immune system with increased secretion of cytokines, COX-2, PGF2 $\alpha$  and PGE2, causing inflammation (Silva et al., 2012; for review: Fieni et al., 2014; Hagman, 2014).

#### *Clinical signs*

Pyometra is a disease frequently occurring in older bitches. After evaluation of animal insurance records in Sweden, Eggenvall et al. (2001) stated that 23-24% of intact bitches will develop a pyometra until the age of 10 years. Dependant on the degree of inflammation and intoxication, and dependant on complication by beginning systemic inflammatory response syndrome (SIRS), clinical symptoms will be very variable. Depression of the general health status, fever, vomiting, diarrhoea, polyuria / polydipsia, abdominal pain and mucopurulent, purulent or sanguinopurulent vaginal fluor may be present (Hardy and Osborne, 1974).

#### *Diagnosis*

Diagnosis aims to quickly differentiate between beginning CEH/pyometra and advanced pyometra complicated by intoxication, systemic inflammatory response syndrome (SIRS) and sepsis, the latter concerning



half of the diseased dogs (Smith, 2006; Hagman, 2014). The usual diagnostic possibilities like vaginoscopy, cytology, sonographical examination and x-ray can be supplemented by new diagnostic tools, recently summarized by Hagman (2014). Typically, abdominal sonography will reveal an enlarged, fluid filled uterus with sometimes thickened, sometimes thinned endometrium, dependant on the degree of CEH and fluid filling. In these cases a blood picture should be performed and in most cases will reveal leucocytosis, neutrophilia and left shift, furthermore normocytic, normochromic anemia and decreased albumin concentrations (Hardy and Osborne, 1974; Feldman and Nelson, 1989; Wheaton et al., 1989; Gandotra et al., 1994; Johnston et al., 2001). To better assess critically diseased patients, measurement of the concentration of acute phase proteins (AAP) has been proven useful (Fransson et al., 1997). The C reactive protein was significantly increased in dogs with pyometra and SIRS due to sepsis and may be of prognostic value (Jitpean et al., 2014; Karlsson et al., 2013). In cases with beginning endotoxemia and/or sepsis, organ dysfunctions especially concerning the kidney may develop. Clinically, the dog's health status will quickly deteriorate; polydipsia, polyuria and increasing proteinuria are the consequences of increasing renal failure. In the liver, cholestasis caused by endotoxins may cause disseminated intravascular coagulation and thrombocytopenia (Hardy and Osborne, 1974). Recently, in SIRS positive bitches, significantly higher concentrations of prostaglandin(*PG*)*M*, a  $PGF2\alpha$  metabolite, was found than in healthy control bitches (Hagman et al., 2006; Karlsson et al., 2013); according to Hagman et al. (2006), differentiation between CEH/mucometra and pyometra was best, when measurement of concentrations of PGM was combined with the percentage of band neutrophils. Furthermore, a post-operative decrease in C reactive protein and PGM was associated with a good clinical outcome (Hagman et al., 2006). Volpato et al. (2012) assessed in bitches with open and closed pyometra increased *lactate* concentrations, indicating tissue hypoxia and hypoperfusion in high-risk patients, however, Hagman et al. (2009) did not measure significantly increased values in pyometra patients with SIRS; pre-operative increased lactate levels are therefore not supposed to indicate SIRS.

### *Treatment*

As described under CEH, the conservative treatment of uterine diseases shall be restricted to defined cases. Early stages of pyometra may be treated, provided the endometrium is not too thickened and interstratified by cysts, no ovarian cysts are present, the cycle is still regular and no signs of intoxication are detectable. Since recidives are frequent, the uncomfortable and long treatment stressing the bitch is mostly restricted to breeding bitches; breeding successfully treated bitches in the next heat was shown to prevent recidives during the following 4-6 cycles (Niskanen and Thrusfield, 1998). Best results were obtained after treatment with the anti-progestin aglepristone, eventually combined with natural or synthetic prostaglandins ( $PGF2\alpha$ ). Concerning aglepristone, different protocols with variable success rates have been published; to summarize, in bitches with metritis or pyometra, resolution of the uterus was achieved in most bitches within 4 weeks; when treatment was combined with prostaglandins, resolution was achieved quicker and the success rate increased (Blendinger et al., 1997; Breikopf et al., 1997; Fieni, 2006). According to Fieni et al. (2014), two s.c. injections of 10 mg/kg aglepristone 24 h apart followed by a second injection after 8 days and if necessary (as proven by sonographical examination), by a third injection after 15 days proved to be optimum; especially when combined with synthetic  $PGF2\alpha$  (1  $\mu$ g/kg) from day 3 to 7 of treatment. This treatment must be combined with broad spectrum antibiotics like amoxicillin-clavulanic acid, intravenous application of fluids and not nephrotoxic NSAIDs. We recently evaluated the use of intravaginally applied PGE1 (misoprostol) in bitches to accelerate abortion. In 7 bitches treated during the post-implantation and mid gestation stage of pregnancy, application of aglepristone (10 mg/kg s.c. on two consecutive days) and misoprostol (MIS, 200  $\mu$ g for bitches with  $\leq 20$  kg bw, 400  $\mu$ g for bitches with  $\geq 20$  kg bw, daily intravaginally until completion of abortion) lead to termination of pregnancy within 6 days in all bitches (Agaoglu et al., 2014). During an ongoing study we now evaluate this protocol for conservative treatment of pyometra in bitches.

### *Prognosis*

Similar to CEH, the outcome depends on the clinical findings. Cases with beginning intoxication and signs of SIRS as well as multiple organ dysfunctions have a poor prognosis, especially when thrombocytopenia and anemia indicate disseminated intravascular coagulation (for review see Hagman, 2014). Concerning fertility prognosis after conservative treatment, the incidence of recidives is high. However, Fieni et al. (2014) reports about no occurrence of recidives during the 3-4 years following conservative treatment, which was confirmed by others (Gobello et al., 2003).

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