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CLINICAL ASPECTS OF UTERINE DISEASE IN THE BITCH AND QUEEN

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Introduction
The diagnosis of the various aspects of uterine pathology may be a challenge for the veterinary surgeon. Since this is essential for proper treatment and especially if we want the bitch remain fertile. Without doubt the valuation of the different disorders that can affect the uterus will directly affect the clinical success.

1.- More frequent uterine cystic lesions:
The most common cystic lesions in the uterine bitches are serous cystic inclusions, adenomyosis, endometrial polyps, mesonephric duct remnants cysts and cysts associated with endometrial hyperplasia (hyperplasia and CEH pseudo-placentational).
The CEH is the most frequent and often associated with pyometra.

The cysts which develop from the endometrium (CEH), which vary greatly in size, number, distribution, histology and clinical significance. The CEH is a common and important injury because can progress to pyometra.

Reactivity of the canine endometrium:
It has been shown that during the lutheal phase of the cycle of the bitch, the endometrium is very sensitive to mechanical stimulation or the presence of foreign material placed inside the uterine lumen. Nomura et al. studies on the natural sensitivity and response of the endometrium during the lutheal phase, in which different uterine suture materials like silk, olive oil, barium, uterine tissue and the bacteria E.coli were introduced surgically into the uterine lumen.

The role of hormones and their receptors:
Models of CEH-P have been proposed in which responsibility for the complex is put on administration of hormones or combined treatments of various hormones. The concentration of progesterone in bitches with CEH is not too high, but the administration of progestagens, especially after oestrogens, predisposes to the syndrome CEH / P. Although the oestrogen and progesterone receptors can be modified by the experimental administration of steroid hormones, it has been suggested that changes in hormone receptors are implicated in the pathogenesis of the syndrome CEH / P.

Endometrial polyps:
These are small endometrial glandular aggregates that, due to stimulation by the deposition of interstitial tissue, protrude and grow from the endometrial wall. Usually they are small in number, are small and do not cause serious consequences unless they grow a lot and occlude the uterine lumen.

Types of cysts from other non-uterine endometrial tissues:
They can be congenital (from the embryonic duct system of the male) developed (adenomyosis of myometrium) or acquired (serous cysts of the peritoneum) and can be mistaken for an embryonic vesicle and pregnancy. There are differences depending on the location, number and size.

-Mesonephric duct remnants cysts:
They are structures that remain after the development of the embryonic part of the male ducts on the horns or the body as smooth cysts of variable size (typically less than 1 cm) near the wide ligament.

Adenomyosis
Presence of ectopic endometrial tissue within the myometrium or the uterine wall. They may be small, similar to endometrial glands or larger covered in endometrial epithelium, this layer can atrophy or even lead to an image of “Swiss cheese” drawn into the uterine wall.

-Serosal cysts:
Initially they are reactive areas of the same kind that lead to thin wall cysts that protrude from the surface. They can be single or multiple, and often appear in groups on any area of the uterine horns or body. They contain clear viscous liquid. They are common in dogs after caesarean section, when the uterus has been over-manipulated.

-Serosal cysts:
Embryonic vesicles can be mistaken for cystic lesions. Pregnancy should be considered if you have uterine cysts or blisters with fluid in it.

-Endometrial hyperplasia like maternal placenta tissues (EHP, pseudo-placentational endometrial hyperplasia)
A second form of endometrial hyperplasia was presented 100 years ago, and although it is described in textbooks, it is not widely accepted by clinicians and pathologists. In this case, the endometrium will respond to stimulation with a highly organized remodelling very similar histologically to sites of placentation in the endometrium during a normal pregnancy. These lesions are very different from CEH and are known as "deciduoma", endometrial hyperplasia in pseudopregnancy although the most accepted is the name of EHP.

Conclusions
Cystic lesions in the canine endometrium are common and can be distinguished based on their location, distribution and morphology. Proliferative endometrial changes may lead to cystic formations that can lead to injury with harmful effects on reproduction.

The endometrium is going to change much during the normal oestrous cycle and during pregnancy. On the other hand, it is asserted that there are two types of endometrial hyperplasia in the dog, and both are pathological, while in one there was an increase of cystic endometrial glands (CEH) in the other (EHP), a transient response similar to the remodelling of endometrial zones of placentation during pregnancy. These two injuries are different in terms of appearance, pathogenesis and clinical significance and should be differentiated by the clinical veterinarians.

2.- Pyometra, hydrometra, haematometra y mucometra
Introduction:
The most common uterine disease in the bitch, cystic endometrial hyperplasia, has been linked with pyometra, haematometra or hydrometra. These diseases can be distinguished by their systemic effects, i.e. pyometra, particularly the closed one, is life threatening condition for the animal, however the others are produced by the accumulation of different types of fluid, always sterile, and none of them has significant systemic signs.

Canine pyometra is a disease that affects nearly one quarter of the non-castrated bitches with less than 10 years of age. It is very important to the veterinary clinic a rapid diagnosis and proper treatment to prevent serious consequences.

Definition:
Pyometra by definition is the accumulation of purulent material within the uterine lumen of non-neutered bitches that usually occurs during or immediately after the period of progesterone dominance. Traditionally it has been thought that the sub-acute endometritis leads to cystic endometrial hyperplasia (CEH) and then the predisposed females develop pyometra. Other studies however suggest that, due to differences in clinical and histopathological of the CEH and pyometra, they should be classified separately. It is common to see the pyometra defined as complex endometritis / CEH / pyometra. Pyometra is classically a disease of the diestrus and can be of two types: open cervix or closed cervix, the latter being a surgical emergency that requires prompt intervention. The mucometra, hydrometra and haematometra are often associated with the CEH and the type of fluid is going to differentiate them of the pyometra:
- The mucometra is an accumulation of sterile intraluminal fluid and mucus.
- The haematometra is an accumulation of sterile bloody fluid
- The hydrometra is an accumulation of sterile watery fluid
Pyometra will further differentiate the post-parturition metritis in terms of pathogenesis, clinical signs, treatment and prognosis.

Epidemiology:
Pyometra affects adult dogs (one in four before the age of 10), which have had many cycles and average
There is increased incidence in nulliparous females (up to 75% of cases) and over 4 years 1 Pyometra may also occur in prepuberlal bitches during anoestrus or during pregnancy. In cases that pyometra is diagnosed during anoestrus (approximately one third of all cases of pyometra) is not known if the animals were observed after the end of the normal lutheal phase or if it has been, at least in some animals, a premature shortening of the lutheal phase, for example induced by the endogenous production of prostaglandines in response to a uterine inflammation2 There was no association between pseudo-pregnancy and pyometra. 1 The importance of factors such as nulliparous females, irregular oestrous cycles or pseudo-pregnancy have not been demonstrated yet2 As predisposing factors for the pyometra stand out treatment with oestrogen and progestagens and to be in the diestrus stage. It is therefore important to know the date of the last heat for a correct differential diagnosis. Hormonal therapies with progestagens to remove the heat, or oestrogens to induce it or to abort may explain the development of pyometra in bitches young. In addition, females with abnormalities in the vagina and vaginal vestibule like septa may also predispose to pyometra. 1 There are more predisposed breeds like Rottweiler, Saint Bernard, Chow Chow, Golden Retriever, Miniature Schnauzer, Terriers, Collier ... however there are other breeds with lower risk for suffering it such as German shepherds, the Dachshund and other hounds. Other studies however show that there is no racial predisposition. Pyometra should be included in the differential diagnosis of non-castrated females with compatible symptoms.

Pathogenesis
CEH develops as a consequence of repeated stimulation by progesterone during the lutheal phase of the oestrous cycle. Although it is thought to predispose to pyometra, both can occur independently of the other1 Although CEH usually precedes the development of pyometra, the CEH does not inevitably progresses to pyometra in all bitches, the same way, while all the bitches developed CEH with age, only some of them develop pyometra2 The current work of Nomura et al. and Koguchi suggest that the classical sequence of progesterone that leads to the CEH and then this leads to pyometra is not correct and that the direction can be reversed with the bacterial infection as an initiator. Sub-clinical infection or a uterine endometrial irritation by foreign bodies during the end of oestrus or early diestrus may stimulate an exaggerated hypertrophy-hyperplasia of the endometrium, similar to what occurs during the implantation ("decidual reaction "). The resulting increase of endometrial glandular secretions and epithelial cells may initiate the development of pyometra or mucometra, depending on whether the fluid in the womb is sterile or is contaminated with bacteria. This hypothesis is supported by experiments showing that a number of foreign substances applied in the uterus in the lutheal phase can cause the proliferation of endometrium3 This will explain the cases of pyometra in female bitches without CEH. Knowing the role of progesterone, it is interesting to know that there are bitches with pyometra and basal levels of plasma progesterone, in these cases that triggers he disease would be the inability of a degenerated uterus to contract or failure of the cervix to relax2. Furthermore, the CEH is also associated with mucometra as it can lead to endometrial thickening, and consequently to the accumulation of viscous fluid in the uterus (mucometra). During diestrus, progesterone produces an increase in the activity of secretory endometrial glands, endometrial thickness increases and decreases myometrial contractility therefore can be the cause of the functional closure of the cervix and of inhibiting the drainage of uterine exudates. These effects would accumulate after several cycles and this would explain the higher incidence in females of middle and advanced age.

Progesterone also will cause a type of cellular immune-suppression. This reduced local immunity together with uterine favourable conditions for microorganisms described above, is used by the bacteria to multiply rapidly. The bacteria most frequently isolated in cases of pyometra is Escherichia coli, but can also be found Staphylococcus aureus, Streptococcus spp., Pseudomonas spp., Proteus spp. All of them migrate from the vagina to the uterus and usually appear in CEH’s of the animals. These bacteria have also been isolated from vaginal cultures in healthy bitches 2 Bacterial contamination of the uterus occurs at the beginning of diestrus, when the cervix is still open and, in cases of CEH, the secretionns cannot be eliminated, leaving the opportunistic microorganisms a perfect environment to colonize and proliferate. E. coli is particularly dangerous in cases of pyometra due to the release of endotoxins that can cause septic shock. Such bacteria adhere specifically to the binding sites in the endometrium, previously stimulated by progesterone via the "uropathogenic virulence factor" (UVF) which induces the synthesis of genes such as pap, sfa, hly A, cnF1 and fim. It has been shown that these genes promote the pathogenesis of human E. coli, providing the union with the epithelium 2 Oestrogenic stimulation previous to the predominance of progesterone is also a key component of the pathogenesis, but it has been shown experimentally that exposure of the endometrium to oestrogen alone does not cause pathological changes or significant changes in the tissue .1 Although the association between pyometra and diestrus has been established is not known exactly the mechanism. Some studies suggest that excessive or prolonged exposure to progesterone is responsible for susceptibility to pyometra, and therefore could be experimentally induced by administration of exogenous
Clinical signs and physical exam:
Clinical signs of pyometra in bitches will depend firstly on whether the cervix allows sufficient drainage of fluid or pus.
- In case of open pyometra, the typical signs are: malodorous vaginal discharge, bloody or mucopurulent. They are not as severe as those with closed pyometra, and the onset of infection may not show any other sign that the vaginal discharge. Other non-specific signs are: lethargy, depression, inapetence to anorexia, polyuria / polydipsia, vomiting and diarrhea.
- In case of closed pyometra, bitches are severely ill, with very marked signs of depression, lethargy, poor appetite and often abdominal distension. They are often dehydrated, septicaemic, toxaeamic and even shock. Fever may or not (often) be present, in case of toxaemia they suffer of hypothermia. It is common to observe no vulvar discharge although fortunately in some cases there will be some kind of vaginal discharge.

- Vomiting is the most common sign in bitches with severe disease. Polyuria-polydipsia are often cited as typical signs and are associated with renal deterioration characteristic of the disease, but still these clinical signs are not consistent because they are in less than half of the bitches with confirmed pyometra.
- Pyometra cause varying degrees of systemic disease, while the mucometra does not cause clinical signs. Both can cause a palpable enlarged uterus due to accumulated fluid.

In case of pyometra, the uterus size is inversely proportional to the degree of cervical opening. If pyometra is suspected palpation needs to be done gently to avoid uterine rupture because the wall will be severely weakened.

The mild CEH as the mucometra will not give important clinical signs, only sterile vaginal discharge and infertility problems because the endometrium is altered.

Diagnostic Findings:
- Complementary methods:
The cytological examination of vaginal discharge is very useful in the early stages as it allows us to distinguish an open pyometra from a mucometra.
In case of pyometra we observe large numbers of neutrophils, often degenerate. In addition to the bacteria can be observed both intra-and extracellular.

- In case of mucometra, cytology shows a small amount of neutrophils, with or without degenerative changes, red blood cells, endometrial cells (with foamy cytoplasm) and a variable amount of detritus.

- In case of pyometra, there are low reds and white blood cell numbers, moderate number of endometrial cells, small amount of mucus and large amounts of detritus.

- In case of haematometra, the predominant cell type is the red blood cells, low white blood cell count, low to moderate amount of mucus, small number of endometrial cells and minimal to moderate amount of debris.

You can also do an exam with vaginoscope.
The enlarged uterus can be felt, but is more reliable to use the ultrasound to make the final diagnosis.
- Haematology y biochemistry:

A common finding in females with pyometra is leukocytes, more important in the closed cervix. The differential counts shows, a neutrophilia with left deviation, presence of toxic neutrophils and monocytosis.
This is not always fulfilled because in 25% of cases, the bitches are presented with a leukogram within normal values.
In some cases, they have a moderate normocytic normochromic anaemia(due to bone marrow functionality suppression by the disease).

In biochemistry can be observed: hyperproteinemia (for dehydration) hypergamaglobulinemia (for chronic antigenic stimulation) and hypoalbuminemia, metabolic acidosis, increased serum alkaline phosphatase (in the 50-75% of cases) and sometimes moderate elevation of ALT (alanine aminotranferase) reflecting hepatocellular damage or the decrease of the hepatic circulation by dehydration.

Usually the serum urea and creatinine levels are increased, but we can see a pre-renal azotemia due to dehydration.

Urianalysis2
The findings are not very useful and dehydration affects the urinary density.
The endotoxemia will cause a typical renal disease: glomerular filtration is reduced and the tubules are unable to concentrate urine (endotoxins desensitized the tubules to the ADH "Secondary nephrogenic diabetes insipidus"), so urinary density will decrease and we will have clinical signs of PU and PD compensation.
Sometimes we can find a urinary tract infection by the same bacteria causing the uterine infection.
In the case of mucometra, biochemistry, haemogram and urianalysis appear normal except for a possible mild regenerative anaemia.
The cystocentesis is not recommended in dogs suspected of pyometra because there is a high risk of perforation of the distended uterus.
Furthermore, intra-vaginal infusion of natural prostaglandines once or twice a day has beneficial effects and less action time, it has been shown to have greater capacity to induce uterine contractions that are preferable (dinoprost ®) to analogues (cloprostenol ®). Although the natural tend to have more side effects, the synthetic prostaglandines (PGF) are not completely clear when used alone or in combination with other drugs.

- Synthetic prostaglandines: luteolysis, cervical opening and uterine contractions:
- Prevention of the effects of progesterone inducing luteolysis and avoiding its join to the receptors, by prostaglandines alone or associated with dopamine agonists or antagonists of progesterone receptors.
- Encouragement cervical relaxation in closed pyometra to allow the expulsion of uterine contents through prostaglandines or progesterone receptor antagonists.
- Induction of uterine contractions and emptying of the uterus, through the use of PGF or indirectly with progesterone receptor antagonists.
- Inhibition of bacterial growth and development through the administration of broad or specific spectrum antibiotics.
- Improvement of regeneration if uterine degeneration, through a prolonged anoestrus, for example by administering an agonist of the androgen receptor mibolerone.

Luteolysis, cervical opening and uterine contractions:
The first objective is to stabilize the patient by eliminating the effects of progesterone directly with luteolysis (prostaglandines break the corpus luteum or dopamine agonists which inhibit prolactin, and this also cause luteolysis) or indirectly using the blockers of progesterone receptor (agluptropristone ®).

- Prostaglandines (PGF):
The results are effective unless large doses are used. Repeated administration of prostaglandine F2α causes luteolysis, which decreases the plasma concentrations of progesterone. In turn induces relaxation of the cervix (functional opening), the drainage of the uterine secretions, and even has a spasmogenic action in the uterus favouring expulsion of fluid. Its use is not permitted in some countries. The treatment consists of doses of 10-50 mg / kg SC or IM route, three to five times daily for 3-7 days. Can be used alone or in combination with other drugs. Extreme caution in calculating the dose is needed, because the therapeutic index is very small and the side effects are severe when using high doses, are dose dependent and there is risk of uterine rupture, especially in cases of closed pyometra, and other side effects such as salivation, vomiting, diarrhoea, wheezing, pyrexia ... to shock and death.

Protocol: 10µg/ml five times during the first day, increasing to 25µg/ml five times the second day and reach 50µg/ml the third day, given three to five times a day for the rest of the treatment Natural prostaglandines are preferable (dinoprost ®) to analogues (cloprostenol ®). Although the natural tend to have more side effects and less action time, it has been shown to have greater capacity to induce uterine contractions that synthetic.

Furthermore, intra-vaginal infusion of natural prostaglandines once or twice a day has beneficial effects and...
Dopamine agonists:
Luteotropic most important hormone in the bitch is prolactin. These are drugs such as bromocriptine or cabergoline. Usually cabergoline is chosen first because not only has barely no side effects and is administered once daily, unlike bromocriptine that is used two to three times a day. The administration of repeated doses of inhibitors of prolactin from 25 days after ovulation achieves a rapid and permanent reduction in blood levels of progesterone. This effect has been used as an abortive in unwanted pregnancies. Now it is also used combined in protocols with low concentrations of prostaglandines with success in the treatment of pyometra for advancing luteolysis.

Combination of prostaglandines y dopamine agonists:
When using the combination, progesterone serum lows in 24-48h, while low doses of prostaglandines alone will take 3-4 days on lower levels of progesterone. In addition, the cervical opening is observed at 24 hours, up to two days using the combination, if we use the PGF alone will take several days. The combined treatment consists in cabergoline $5 \mu g/ml$ plus cloprostenol every three days The side effects lasted up to 1 hour after administration of prostaglandine and its incidence was decreasing with successive doses. They can be reduced even further if the dose of cloprostenol is decreased $1$ or $2.5$ mg / ml, but even if it has the same luteolytic activity probably would require more doses per day. The effects are similar using the natural prostaglandines such cabergoline to $5 \mu g/ml$ PO once daily for 7d than using bromocriptine to $25$ mg / ml PO three times daily for 1 week.

-Progesterone receptors antagonists:
In countries where it is allowed, its use has been proposed as a treatment of pyometra with controversial results. These are drugs such as mifepristone or aglepristone that bind to progesterone receptors blocking them so they are inactive, this CEEhho induces luteolysis that causes cervical relaxation. It is no known the direct effect to induce uterine contraction, although there are some hypotheses that these uterine contractions are induced indirectly by endometrial inflammation associated with pyometra (no safe enough for use in single treatment). These combined with prostaglandines lead to uterine contractions and induction of luteolysis. Aglepristone, which is not available in the U.S., suppresses the action of progesterone during pregnancy (use as an abortive, relax the cervix and induces labour). This product has been used successfully in the treatment of uterine infections associated with high levels of serum progesterone. The exclusive use of aglepristone is effective in the treatment of pyometra and can induce the opening of the cervix in some cases of closed pyometra, but the combination with cloprostenol was more effective for treating any type of pyometra.

-Prostaglandine E:
During oestrus, the increase in oestradiol (and oxytocin) during the pre-ovulatory period may stimulate the increased synthesis of PGE and its receptors that are going to remodel the extracellular matrix of the cervix and thus produces relaxation. In sheep the use of misoprostole improves cervical permeability at the end of oestrus. Isolated results, without scientific evidence of effectiveness, suggests the use of intravaginal misoprostole to promote cervical relaxation.

-Antimicrobial treatment:
The first conservative method developed, medical therapy was based on the use of both systemic and local antibiotics. During any of the previous protocols should be given a broad spectrum antibiotic. The ideal is to do a culture and antibiogram to see the sensitivity of bacteria isolated from vaginal discharge before starting antimicrobial treatment. The uterine contraction associated with the treatments, can potentially cause septicaemia in the case of bitches with bacteremia. The most effective antibiotics are: Amoxicillin, amoxicillin-clavulanate, cephalosporins, sulphonamides ... If administered orally, must take into account the potential vomiting due to injection of PGE. It is further recommended that the therapy is maintained during 10-14 days after recovery of the bitch and then to do a control with an ultrasound, physical examination and blood analysis two weeks after completing treatment of prostaglandines.

-Administration of oestrogens:
It has been traditionally used to relax and open the cervix in addition to increasing uterine contractility. However, it also causes vasodilation and increased initial blood flow to the uterus and this is associated with the absorption of toxins and acute toxaemia thus worsening the situation. Currently it is not used.
Uterine regeneration:
To prevent relapses, especially in animals with clear signs of degeneration in the uterus, you can try extending the anoestrus, postponing the next oestrus, to allow the endometrial regeneration by administration of agonists of the androgen receptor as mibolerone.
Postponing the next cycle about two months (maximum 3), prolong the healing period to facilitate regeneration with reduction of most uterine hyperplastic lesions (CEH).
Method: Start about a month after the end of medical treatment for pyometra and oestrus will appear a few weeks after the cessation of mibolerone.

Incidence of DIC:
It has been observed when treatment was initiated in bitches with chronic disease and there has been no improvement for 3-4 days. More often if the treatment is based on the administration of antagonists of the progesterone receptor without prostaglandines.
It can be prevented through an injection of heparin at the beginning of the medical treatment at a dose of 100-500UI/kg and monitoring the haematological parameters. The effectiveness is uncertain.

Conclusions
The mucometra, hydrometra and especially pyometra are diseases that should be included in the differential diagnosis of non-neutered females with clinical signs consistent with these diseases.
Clinical signs, history and physical examination are useful to diagnose them.
The differentiation between mucometra, hydrometra, haematometra and pyometra can be done primarily through a smear, but we can also use other methods, such as complete blood count, biochemistry, urianalysis and ecography1.
The supportive treatment is absolutely necessary, such as intravenous fluid therapy to 1.5 - 2 times maintenance rate, and support treatment of kidney, liver and heart functions.
Rupture of the uterus has not been observed using prostaglandines at low doses but it has with larger doses 100μg/ml, spontaneously or during treatment.
When using prostaglandines alone or associated with dopamine agonists or progesterone receptor antagonists, the condition of the animals usually improves within the first 48h and further increases the amount of discharge at 24 hours, changing it from purulent or serosanguinolent to serosa and terminates at 4-7 days.
Respect to changes in blood tests, they return to normal within the first 7 days after a hysterectomy and after 10-15 days of the conservative treatment.
The incidence of relapse after medical treatment is not known exactly, although it is decreasing as the combination protocols of drugs are optimized.
Fertility after treatment was considered good and conception rates vary from 50 to 75% depending on the age of the animal (most successful in young animals).

Bibliography