RECENT ADVANCES IN CANINE PYOMETRA

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Canine pyometra is a common pathological affliction of intact bitches (Predominantly nulliparous bitches) depicting pus in the uterus (Chastain *et al*., 1999). The early changes due to disease are generally not so noticeable and hence the disease generally remains undiagnosed till 4 weeks.

Kustritz (2010) categorised pyometra as two step process:

A. *First Step is Cystic Endometrial Hyperplasia (CEH)*: Thickening of uterine endometrial lining occurring of canine. Escherichia coli subtypes are the most common isolates found in infection cases. Pyometra is most commonly reported in intact bitches, which suggest that pregnancy may have some protective secondary to repeated oestrus cycles. Estrous cycle in bitches is unique with high serum estrogen followed by elevation in progesterone concentration after every cycle promoting hyperreactivity of endometrium and gradual cystic hyperplasia: Development of cystic endometrial hyperplasia is continuous but it remains a mystery why some bitches develop pyometra with minimal CEH while others with severe CEH do not.

B. *Second step is infection*: Infection generally occurs due to microorganisms that are normal vaginal microflora effect probably at endometrial level.

Pathophysiology of Pyometra:

Normal plasma progesterone concentration in anoestrus bitches is less than 0.5 ng/ml (Nelson *et al*., 1982). The progesterone concentration post-ovulation increases for approximately 2 months generally and exceeds 40 ng/ml. The repetitive cyclicity of bitches involves a period of uterine estrogen stimulation followed by prolonged intervals of progesterone dominance (Dadarwal, 2007). Estrogen promotes endometrial growth, vascularity and oedema, cervical relaxation and dilation and migration of polymorphonuclear leucocytes to the lumen (Hardy and Osborne, 1974). While progesterone stimulation results in proliferation and secretory activity of endometrial glands, maintains functional closure of cervix and inhibits myometrial contractility. Normal vaginal microfloral-bacteria ascend from the vagina to the cervix during the proestrus and estrus phase. The altered uterine environment prevents complete expulsion of organisms before end of oestrus resulting in entrapment of organisms in the uterus in di-estrual bitch due to closure of cervical Os. Bacterial growth in progesterone primed uterus is further supported by leucocytes inhibition and secretions of endometrial glands. Progesteronal effect is further amplified by estrogen up-regulation of endometrial progesterone receptors. The endometrium thus becomes hyper reactive, exacerbating the hyperplasia. Infection develops with creation of pool of purulent intrauterine fluid. The factors determining cervical patency is still a mystery.

According to De Cock *et al*., (2002) insulin-like growth factor I located in and around the epithelial cells of endometrium in dogs with CEH may play an important role in development of pyometra.

Renal complications are common sequel to pyometra. Endotoxins released from the cell wall of gram negative bacteria inhibit normal renal tubular function (Kustritz, 2010). These changes being reversible are controlled as soon as infection is taken care.

Stages of Disease:

Dow (1958) histologically classified canine endometrial hyperplasia-pyometra complex into four stages:

1. Stage-I (Uncomplicated CEH): This stage is marked by thickened endometrial surface with multiple irregular cystic lesions giving it cable stone appearance.
2. Stage-II: Infiltration of plasma cells occurs in cystic endometrial tissue.
3. Stage-III: (CEH overlying acute endometritis): Gross lesions include ulceration and haemorrhage of

endometrium and uterus and may contain red-brown to yellow-green pus. Acute endometritis is characterized by congestion, oedema and superficial and deep infiltration of neutrophils into endometrium. Myosis may also be seen in some cases.

4. Stage-IV (CEH with chronic endometritis): Open cervix pyometra is characterized by collapse and grossly thick walled uterus wall with minimum discharge. The endometrium is atrophied while the myometrium is hypertrophied and fibrotic. While in closed cervix pyometra both endometrium and myometrium of distended uterus are atrophied.

Bacteriology:

Mostly the infection ascends from the vagina through the patent cervix into uterus during the proestrus and estrus phase and is cleared off within 5 days post inoculation (Dadarwal, 2007). But in females with CEH the expulsion of organisms is not complete before end of estrus due to which secondary infection flares up. These organisms infecting uterus are normal inhabitants of vagina. E. Coli is found to be most common (70% cases) while the other isolates like streptococcus Spp., Staphylococcus Spp., Klebsiella Spp., Proteus Spp., Pseudomonas Spp., Corynebacterium Spp., Enerococcus Spp., Pasteurella Spp., Serratia Spp., Haemophillus Spp., and Bacillus Spp., are also reported (Vandeplassche *et al*., 1991).

Clinical Signs:

History in pyometra cases reveals that the bitch was in oestrus a few weeks (2-12 weeks) prior to illness. Clinical signs in pyometric bitches vary with cervical patency.

At times in open cervix pyometra continuous sanguineous to mucopurrulent vulval discharge may be seen for years. Colour and consistency of the discharge vary considerably. In most of the cases light chocolate brown coloured discharge of thin consistency with its characteristic odour may be seen. While in some cases it may be yellow coloured with blood tinge with watery to creamy consistency. Closed cervix pyometra cases can become open at any time but continuously discharging open cases rarely become closed one. Sometimes no vaginal discharge is seen despite owner's history; this may be due to flushing of vestibular area from recent urination. Elevated body temperature is common feature of closed cervix pyometra while body temperature may be normal or slightly elevated in open cervix pyometra. Temperature may be subnormal in toxaemic cases. Peri-vulvar tissue is discoloured or scalded with vulvar enlargement.

In advanced cases polydypsia may be seen due to reduced permeability for water in the distal convoluted tubule of the kidney (Asheim, 1964). Renal dysfunction results due to formation of immune complexes (Sandhlom *et al*., 1975). Other symptoms include lethargy, depression, inappetence, Polyuria and vomiting. Abdominal distension is a variable feature.

If the condition is not life threatening and animal is valuable for breeding purpose or if surgical intervention is not possible due to intercurrent disease than medicinal regimes can be considered. Uterine fluid draining by use of catheter via cervix and by surgery (Hysterotomy) drains has been tried by transcervical route by different workers (Gourley, 1975). Since pyometra is a disease of luteal phase use of prostaglandins to initiate luteolysis as well as to initiate uterine spasmogenic action has been used successfully for treatment of open-cervix pyometra (Gilbert *et al*., 1989; Wheaton and Barbee, 1993).

Diagnosis:

Diagnosis of pyometra is confirmed when the appropriate clinical signs are reported by the owner are present in conjunction with abnormalities with physical examination, laboratory examination, radiographic evaluation and ultrasonography. Diagnosis of stump pyometra is difficult (when discharge is not present) and refers to inflammation and bacterial infection of the post-Ovariohysterectomy remnant of uterine body. This remnant tissue can result in occurrence of oestrus cycle, progesterone secretion, uterine secretion and inflammation. The following methods are commonly used for diagnosis of pyometra in canines.

A. Abdominal Palpation: Care must be taken while manipulating the febrile uterus. Abdominal palpation in open-cervix pyometra cases may reveal thickening of uterine cornua, slightly

irregular and turgid structures from 1 to 3 cm in diameter. Some areas of uterine horns are turgid and solid to palpate while others distended with pus may be indistinguishable from the surrounding bowel. In closed cervix cases abdominal palpation may reveal greater degree of abdominal enlargement.

B. Radiography: It is less traumatic means to visualize the status of uterus as compared to abdominal palpation but it can only gives brief idea about uterine enlargement but cannot be used to differentiate diseased animals from pregnant animals. Radiographic visualization of abdomen for confirmation of pyometra reveals fluid-dense tubular structure in ventral and caudal abdomen displacing loops of intestine dorsally and cranially. Radiographic examination will also reveal presence or absence of peritonitis from a uterine rupture and retained fetal tissue from previous pregnancy.

C. Haematology: Leucocytosis and neutrophilia (specially in closed cervix pyometra) with regenerative shift to left and monocytes is observed in cases of closed cervix pyometra and is less marked in cases of open cervix pyometra.

D. Cytology: Cytology of vulvar exudates reveals degenerative polymorphonuclear cells (PMNs), bacteria and non-cornified epithelial cells (small intermediate epithelial cells, large intermediate epithelial cells).

E. Ultrasonography: Ultrasonography is a valuable aid in diagnosis of pyometra especially when radiographs are inconclusive like in cases of stump pyometra. It permits the operator to see and identify the free fluid inside the uterus. Uterus reveals increase in thickness (relatively hypoechoic) and diameter and folding on itself so as many sections of each horn may be imaged in a single plane. Uterine diameter may vary depending upon whether the cervix is open or closed. Uterine lumen is grossly dilated with anaechoic fluid with small echogenic particles.

Pregnancy can easily be identified and definitively differentiated from pyometra 24 to 25 days post ovulation. Limitations of ultrasound are that it cannot be used to determine if intrauterine fluid is purulent.

Treatment:

Choice of treatment (medical or surgical) is made on the basis of patient's clinical condition and owner's intention regarding future breeding. But Ovariohysterectomy is treatment of choice (Maclntire, 2004) in most of the cases unless the animal is valuable for breeding purpose. Surgical removal of the infected uterus results in immediate clearance of endotoxins from the body along with return of WBC count returning to normal by 7 days post-surgery.

Medical therapy is indicated (Kustritz, 2010) only when:

- Cervix is patent.
- Azotemia is absent or mild enough to be attributed to dehydration or other pre-renal causes.
- Female dog is of breeding age (less than 6 years)
- Bitch is valuable and is to be used for breeding purpose

Medicinal therapy by different drug like estrogen, androgens, ergot alkaloids, quinine and oxytocin have been tried but failed to show promising results. PGF2a therapy has shown promising results. PGF2a treatment results in contraction of myometrium (immediate effect), Luteolysis (delayed effect) and relaxation of cervix (least consistent effect). However PGF2a should be used with caution in closed cervix pyometra because of risk of expulsion of uterine exudates into the peritoneal cavity resulting in peritonitis. Corpus Luteum in bitches is refractory to PGF2a action for first 1-2 weeks and after 1-2 weeks it takes at least 5 days until luteolysis is achieved.

Medicinal treatment with a combination of antibiotics and prostaglandin F2 alpha can be initiated with following protocol:

- Assessment of uterine size in repeatable manner (abdominal palpation, radiography and ultrasonography).
- Collect vulvar discharge for aerobic culture and antibiotic sensitivity test.
- Initiate treatment with antibiotic like amoxicillin/clavulanate and than change the antibiotic (Quinolones like enrofloxacin or Cephalosporines) if necessary on the basis of culture sensitivity results.
- Measure serum progesterone for initiating prostaglandin therapy. If serum progesterone is less than 2 ng/ml than once daily and if serum progesterone is more than 2 ng/ml than twice daily

prostaglandin therapy is effective for lysis of CL and decrease serum progesterone and initiates uterine contractions.

- PGF2a should be 0.1-0.25 mg/kg once or twice daily subcutaneously. PG treatment should be given till uterine size returns to normal or until there is no visible free intra uterine fluid.
- Antibiotic therapy should be continued for a month or until there is no visible vulvar discharge for at least for a week.

An alternative 7 day natural prostaglandin therapy (94% recovery rate in open cervix and 31 % in closed cervix cases) includes PGF2a treatment at the dose rate of 0.1 mg/kg sub-cutaneously followed by 0.2 mg/kg body wt. on day 2 and subsequently 0.25 mg/kg from day 3-7 along with 14 day antibiotic course. Animal should be revaluated at day 7 and 14 and retreatment should be done in case of persistence of purulent vaginal discharge, fever, increased WBC or fluid filled uterus (Feldman and Nelson, 2004). Breeding in first cycle post-treatment is strongly recommended to avoid the risk of recurrence as pregnant bitches are less susceptible and there is no benefit in skipping a cycle.

Dose dependent side effects of PGF2a therapy have been noticed which decrease and disappear with repeated administrations include restlessness, pacing, hypersalivation, panting, vomiting, abdominal pain or cramping, tachycardia, fever, defecation and uterine evacuation.

Other therapies used include use of antiprogestins and anti-prolactins. Antiprogestins exert their action on female reproductive tract in the presence of progesterone resulting in opening of cervix (day 1-3 after initiation of treatment), stopping the progestative inhibitory effect to myometrial contractions and stopping the progestative immunosuppressive effect. They have no luteolytic effect. Wehrend *et al*., (2003) reported successful treatment of closed cervix pyometra in all the bitches treated with antiprogestin (aglepristone, 10mg/kg subcutaneously 1, 2and 7 or as long as natural progesterone is present, along with antibiotic therapy). Gobello *et al.,* (2003) and Trasch *et al*., (2003) reported that open cervix pyometra can be successfully treated independent of initial progesterone level when a combination of synthetic prostaglandin (Cloprostenol) along with antiprogestin (aglepristone) is used.

Anti-prolactin (Dopaminergic drugs) act via causing luteolysis (delayed action comparable with PGF2a) and blocking prolactin production (if present).

Synthetic prostaglandins (Cloprostenol; 5llg/kg every third day subcutaneously), Antiprolactin/ prolactin inhibitor (Cabergoline; 5 µg/kg once daily per os for 7-10 days) and antibiotics combination has also been found to be successful in treating open- or closed-cervix pyometra (Kustritz, 2010). Fieni *et al*., (2001) reported success rate of 87% and 63% when antiprogstin were used with Cloprostenol and without cloprostenol, respectively.

Supportive therapy depends on general condition and CBC reports. Intravenous fluid therapy (Ringer's lactate/5% dextrose) should be given immediately to minimize the renal toxic effects. Efforts should be made to restore plasma electrolytes and acid-base balance.

H2 blocker like metaclopromide is also indicated in case of vomiting and qastric injury. Antiinflammatory drugs/ NSAIDs are also useful Intravenous fluid therapy along with broad spectrum antibiotics is ideally recommended as it is not always possible to stabilize patients before surgery.

Relapse rate of at least 20 per cent has been reported during the first two years after treatment.

Conclusions:

Canine pyometra is a common pathological condition of intact bitches (Predominantly nulliparous bitches) depicting pus in the uterus. Organisms infecting uterus are normal inhabitants of vagina while E. Coli is found to be most common (70% cases). Clinical signs in pyometric bitches vary with cervical patency. Ultrasonography is an important definitive diagnostic tool. Ovariohysterectomy is the therapy of choice for canine pyometra as high relapse rate upto 20 % in medical treatment has been reported. Medical treatment is not recommended to treat bitches with uterine ruptures and or renal diseases. Medical treatment

has best outcomes in young bitches without antiprogestins is treatment of choice in closed cervix and high progesterone situations. Use of history or signs of ovarian diseases. Use of PGF2a in low progesterone cases or during antiprogestin treatment may improve success rate.

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