



# Detailed Pathophysiological Investigation of Canine Pyometra and the Curative Role of Ovariohysterectomy

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10.18805/IJAR.B-4958

## ABSTRACT

**Background:** Pyometra or cystic endometrial hyperplasia complex in dogs is a hormonally mediated bacterial disease wherein middle-aged bitches are most affected. The current study was carried out in pyometra-affected bitches to determine the alterations in hormonal, histopathological and haemato-biochemical profiles after 14 days of ovariohysterectomy.

**Methods:** Blood samples were collected both from control (n=15) and affected bitches (n=15) showing signs of open cervix pyometra preoperatively and postoperatively on the day of surgery, on the 7<sup>th</sup> and 14<sup>th</sup> day after ovariohysterectomy. Blood samples were subjected to the estimation of endocrinological and hematobiochemical parameters. The ovary, oviduct and uterus were collected for gross and histological observations.

**Result:** The pre-operative serum progesterone (ng/ml) recorded in bitches affected with pyometra were 9-fold higher than controls ( $9.77 \pm 2.64$  vs  $0.61 \pm 0.66$ ) ( $P < 0.01$ ). There was a non-significant difference in the pre-operative ( $414.63 \pm 62.88$ ) and post-operative ( $390.6 \pm 54.20$ ) estrogen concentration and the results indicated a presence of an extragonadal source of estrogen. The enormous endometrial lumen of these cysts contained eosinophilic hazy granular material and tissue debris along with massive infiltration of inflammatory cells, predominantly neutrophils. The findings of the study revealed that progesterone is the major contributory factor and extragonadal sources of estrogen may be present along with hyperplastic changes in the uterine and glandular epithelium in pyometra-affected bitches.

**Key words:** Canine Pyometra, Estrogen, Hematobiochemical, Progesterone, Pathophysiology.

## INTRODUCTION

Pyometra develops because of complex etiological factors which include the hormonal influence of the uterine environment, the virulence of the infecting bacteria with concomitant disability of the bitches to combat the infection or its inflammatory products (Gogoi *et al.*, 2018). The canine endometrium is a complex and dynamic tissue to guarantee embryonic survival, implantation and successful pregnancy. In response to changes in sex steroids, the endometrium undergoes cyclical remodeling, integrating morphological and functional changes which is controlled by cytokines, interleukins and growth factors (Dekel *et al.*, 2010; Somi *et al.*, 2008). Progesterone is responsible for the functional closure of the cervix and relaxation of the myometrium which greatly increases the susceptibility of the uterus to infection. Endometrial hyperplasia is more complicated if the uterus is primed with a high concentration of estrogen. Acute phase proteins blood concentration is known to be elevated 100- to 1000-fold within 24-48 hours after inflammatory irritation which has also been linked with the length of postoperative hospitalization (Fransson *et al.*, 2007).

Besides the well-described clinical signs and systemic effects, information concerning the histopathological, hormonal effects and acute phase proteins after 14 days of ovariohysterectomy are scanty. With this hypothesis, the present study was designed with the objectives to estimate progesterone and estrogen profile in pyometra-affected bitches and study the changes in acute phase proteins, with alterations in haemato-biochemical profile after 14 days of post ovariohysterectomy.

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**How to cite this article:** Gogoi, J., Leela, V., Suganya, G., Shafiuza, M., Vairamuthu, S. and Rajathi, S. (2026). Detailed Pathophysiological Investigation of Canine Pyometra and the Curative Role of Ovariohysterectomy. *Indian Journal of Animal Research*. 60(5): 891-896. doi: 10.18805/IJAR.B-4958.

**Submitted:** 15-06-2022    **Accepted:** 13-12-2022    **Online:** 16-12-2022

## MATERIALS AND METHODS

### Experimental design

The present study was carried out in fifteen clinical cases of pyometra in bitches aged between 2-13 years irrespective

of the breed presented for treatment at the Small Animal Clinic Outpatient unit in Teaching Veterinary Clinical Complex, Madras Veterinary College, TANUVAS. The entire study was conducted for 6 months from August 2017 to December 2017. Fifteen apparently healthy bitches aged between 2-13 years were taken as a control.

Information regarding obesity, breed, age, parity and breeding history was recorded for fifteen pyometra-affected bitches. A thorough clinical examination was also performed on the animals such as the presence or absence of vaginal discharge as evident by visual examination of vulval lips. (Fig 1a), presence or absence of vulval edema (Fig 1b). Each animal was subjected to abdominal palpation for evidence of uterine distension suggestive of pyometra.

#### Ultrasonography studies

All the fifteen bitches on the day of presentation to the clinic were subjected to transabdominal ultrasound scanning (Aquilo® Pro, Esaote Piemedicals) by using a 5 to 7.5 MHz sector probe. All the bitches were subjected to ovariohysterectomy for management of the condition.

#### Collection of blood samples

Blood samples were collected both from control (n=15) and affected bitches (n=15) showing signs of open cervix pyometra preoperatively and postoperatively on the day of surgery, on the 7<sup>th</sup> and 14<sup>th</sup> day after ovariohysterectomy. Serum samples were subjected to hematological and biochemical parameters estimation. A standard Ovariohysterectomy was performed on the affected animals and the ovary, oviduct and uterus were collected and gross observations were made. The uterus was submitted for histopathology.

#### Statistical analysis

The data were subjected to one-way analysis of variance (ANOVA) and post hoc tests Tukey's and Duncan's tests

were performed to analyze the between-group and within-group variations. SPSS software version 20 for windows was used to perform all the statistics.

## RESULTS AND DISCUSSION

#### Ultrasonography results

Ultrasonography examination revealed enlargement of both uterine horns in the bitches which are clinically suspected for pyometra (Fig 2). Sonographically, the lumen of the horns was filled with homogenous anechoic contents with hyperechoic bands in between which presented a fluid-filled pocket-like appearance. In fifteen bitches, the endometrium appeared thick, irregular and within the thickened endometrium there were islets of anechoic foci representing dilated cystic glands and four bitches had mild thickening of the endometrium with very little fluid accumulation.

#### Haematological parameters

There was no statistical difference observed among control and experimental groups in the mean hemoglobin levels, TEC values, or monocyte values, in the eosinophil count (Table 1). Throughout the study period, there was a significant increase in thrombocyte count on the 14<sup>th</sup> postoperative day at the level of  $P < 0.05$ . There was a significant difference observed among the control and experimental groups ( $P < 0.01$ ) in the leukocyte count and lymphocyte count. In the present study before ovariohysterectomy, leukocytosis and lymphocytopenia were the most consistent finding among the bitches affected with pyometra which is in agreement with previous reports by Feldman *et al.* (2000); Dave (2002); Jadhav *et al.*, (2005); Dabhi *et al.* (2009); Jena (2013); Chithra (2013); Shah (2017); Melih *et al.*, 2012. The percentage of neutrophils decreased significantly after ovariohysterectomy indicating the removal of toxins from the bitch's bloodstream ( $P < 0.05$ ).



**Fig 1(a):** Reddish blood discharge in pyometra-affected bitches presented on the first day of clinics. **1(b):** Enlarged vulva in pyometra-affected bitches presented on the first day of clinics.

## Biochemical parameters

### Blood urea nitrogen (BUN) and creatinine

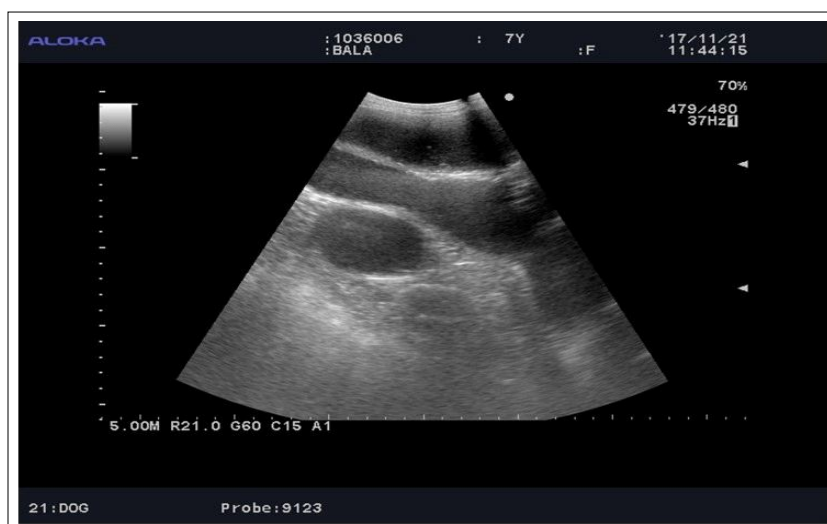
There was a statistically significant difference in BUN and creatinine, AST and ALT concentration between control and experimental groups at the level of  $P < 0.01$  (Table 1). The present findings are in corroboration with the findings of Sharma (2004); Kuplulu *et al.* (2009); Plavec *et al.* (2006); Gupta (2012, 2013); Dabhi *et al.* (2007) and Patil *et al.* (2013) and Shah *et al.* (2017). The increase in the BUN levels during the pre-operative period and day of surgery may be due to the occurrence of Septicemia in pyometra leading to hepatocyte damage and the circulating toxins causing alteration in the cytoarchitecture of hepatocyte resulting in leakage of intra-cytoplasmic contents. Thereby, increasing the serum AST and ALT levels in affected bitches. The level of BUN, creatinine, AST and ALT levels decreased post-operatively indicating that the removal of the pyometric uterus reserves energy metabolism due to the removal of the infection. This may also account for the regeneration of

hepatocytes after the removal of the infection. This implies that early diagnosis and early correction prevent the animal from going in for renal insult and preserve the health status.

### Hormonal concentration

#### Progesterone concentration

There was a statistically significant difference between the control and experimental groups at the level of ( $P < 0.01$ ) in the progesterone concentration (Table 2). In the present study, the level of progesterone was higher during the pre-operative period and on the day of surgery was 9-fold higher than the control groups attributing the source to ovaries, whose activity is disturbed, where its controlling hormones failed to reset their secretory pattern. Moreover, due to its role in blocking myometrial contraction the infection set in resulting in pyometra ensuring its seating in the uterus as flushing of the endometrium contents is impossible. This is advantageous for microbes to proliferate in the given environment and for the propagation of the disease.



**Fig 2:** Ultrasonography showing anechoic pockets and thickened.

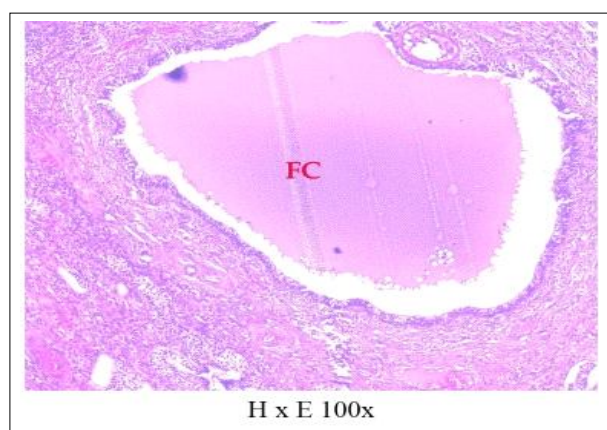
**Table 1:** Haematobiobiochemical concentration (MEAN $\pm$ S.E) of control animals and pyometra-affected bitches (pre-operative and post-operatively).

Parameters	Control	Preoperative	Day of surgery	7 <sup>th</sup> postoperative day	14 <sup>th</sup> postoperative day	F value
Haemoglobin (g/dl)	11.32 $\pm$ 0.541 <sup>a</sup>	12.66 $\pm$ 1.00 <sup>a</sup>	10.70 $\pm$ 1.05 <sup>a</sup>	10.77 $\pm$ 1.05 <sup>a</sup>	11.66 $\pm$ 0.83 <sup>a</sup>	0.881 <sup>NS</sup>
PCV (%)	36.14 $\pm$ 1.81 <sup>a</sup>	32.49 $\pm$ 2.27 <sup>a</sup>	29.26 $\pm$ 2.34 <sup>a</sup>	30.22 $\pm$ 2.34 <sup>a</sup>	31.15 $\pm$ 2.05 <sup>a</sup>	1.501 <sup>NS</sup>
RBC ( $\times 10^6/\text{mm}^3$ )	5.5 $\pm$ 0.30 <sup>a</sup>	5.26 $\pm$ 0.15 <sup>b</sup>	4.6 $\pm$ 0.32 <sup>a</sup>	5.22 $\pm$ 0.42 <sup>a</sup>	5.24 $\pm$ 0.37 <sup>a</sup>	0.731 <sup>NS</sup>
WBC ( $\times 10^3/\text{mm}^3$ )	8.39 $\pm$ 6.74 <sup>a</sup>	27.08 $\pm$ 4.45 <sup>b</sup>	19.92 $\pm$ 4.45 <sup>ab</sup>	13.51 $\pm$ 2.43 <sup>a</sup>	11.95 $\pm$ 1.99 <sup>a</sup>	5.301 <sup>*</sup>
Platelets ( $\times 10^5/\text{mm}^3$ )	1.20 $\pm$ 0.32 <sup>b</sup>	2.08 $\pm$ 0.49 <sup>ab</sup>	1.39 $\pm$ 0.39 <sup>a</sup>	1.41 $\pm$ 0.419 <sup>a</sup>	3.14 $\pm$ 0.52 <sup>a</sup>	3.33 <sup>*</sup>
Neutrophils (%)	72.65 $\pm$ 0.49 <sup>a</sup>	84.50 $\pm$ 2.12 <sup>c</sup>	84.500 $\pm$ 1.90 <sup>c</sup>	79.80 $\pm$ 1.69 <sup>a</sup>	79.40 $\pm$ 1.36 <sup>b</sup>	9.63 <sup>*</sup>
Lymphocytes (%)	20.20 $\pm$ 1.09 <sup>a</sup>	12.20 $\pm$ 1.75 <sup>b</sup>	11.400 $\pm$ 1.933 <sup>b</sup>	17.30 $\pm$ 1.256 <sup>b</sup>	16.40 $\pm$ 0.00 <sup>b</sup>	5.18 <sup>*</sup>
Monocytes (%)	1.90 $\pm$ 0.45 <sup>a</sup>	2.90 $\pm$ 0.54 <sup>ab</sup>	3.20 $\pm$ 0.46 <sup>ab</sup>	3.80 $\pm$ 0.78 <sup>b</sup>	4.20 $\pm$ 0.46 <sup>a</sup>	2.51 <sup>NS</sup>
Eosinophils (%)	1.00 $\pm$ 1.00 <sup>a</sup>	3.800 $\pm$ 0.78 <sup>a</sup>	4.20 $\pm$ 0.46 <sup>a</sup>	3.200 $\pm$ 0.46 <sup>a</sup>	2.90 $\pm$ 0.46 <sup>a</sup>	1.14 <sup>NS</sup>
BUN (mg/dl)	11.07 $\pm$ 0.51 <sup>a</sup>	25.13 $\pm$ 2.74 <sup>c</sup>	20.85 $\pm$ 2.21 <sup>bc</sup>	16.21 $\pm$ 2.01 <sup>ab</sup>	15.03 $\pm$ 2.20 <sup>ab</sup>	6.671 <sup>**</sup>
Creatinine (mg/dl)	0.63 $\pm$ 0.03 <sup>a</sup>	1.20 $\pm$ 0.04 <sup>c</sup>	1.15 $\pm$ 0.05 <sup>c</sup>	0.933 $\pm$ 0.04 <sup>b</sup>	1.02 $\pm$ 0.03 <sup>b</sup>	29.641 <sup>**</sup>
AST (U/L)	23.60 $\pm$ 2.01 <sup>a</sup>	55.48 $\pm$ 4.54 <sup>b</sup>	57.28 $\pm$ 12.09 <sup>bc</sup>	52.19 $\pm$ 4.96 <sup>b</sup>	46.11 $\pm$ 5.14 <sup>b</sup>	4.237 <sup>**</sup>
ALT (U/L)	28.10 $\pm$ 1.42 <sup>a</sup>	37.40 $\pm$ 4.32 <sup>ab</sup>	49.60 $\pm$ 5.71 <sup>ab</sup>	41.05 $\pm$ 4.05 <sup>b</sup>	38.15 $\pm$ 4.21 <sup>ab</sup>	3.401 <sup>**</sup>

An increase in progesterone concentration in pyometra may also be attributed to the inductive influence of estradiol on cytoplasmic progesterone receptors besides the presence of the corpus luteum. Progesterone levels significantly declined ( $P<0.05$ ) fourteen days post-operatively in all animals following the removal of the corpus luteum since ovaries are the main source of progesterone production. The present findings of progesterone levels closely coincided with the values reported by Karmakar *et al.* (2002); Dabhi *et al.* (2007); Gupta (2012) and Shah *et al.* (2016).

### Estrogen concentration

The pre-operative plasma estrogen recorded in bitches affected with pyometra was lower than in the control groups. Serum estrogen (pg/ml) concentration of control and experimental groups did not differ significantly (Table 2). However, with no significant difference, post-operatively its levels did not differ significantly from the pre-operative values with a slight decrease on the day of surgery and on the 7<sup>th</sup> post-operative day and on the 14<sup>th</sup> postoperative day. The 14<sup>th</sup>-day post-operative level was numerically higher even though the classical source of estrogen namely the ovaries were removed. This may be due to the production of estrogen from the extragonadal source of estrogen such as adipose tissues in older and obese dogs. As most of the dogs included in the study were obese. The present findings of estrogen levels closely coincided with the reported value by Dabhi *et al.* (2007); Gao *et al.* (2011); Gupta (2012) also reported elevated plasma estrogen profile in pyometric bitches.



**Fig 3:** Photomicrograph of ovary of pyometra bitch showing a large follicular cyst (FC) in the cortex.

### Acute phase proteins

C reactive protein and serum amyloid concentration of experimental groups did not differ significantly when compared to the control group, though there was a marked increase in C reactive protein on the day of surgery, the 7<sup>th</sup> post-operative day and during the preoperative period (Table 2). The results are in accordance with Dabrowski *et al.* (2007, 2013) and Lakshmikanth *et al.* (2017). After ovariohysterectomy in pyometra-affected bitches, there will be an increase in the production of proinflammatory mediators because of surgical trauma (Christensen *et al.*, 2014) and hence there was a nonsignificant increase in Preoperative CRP concentration. In dogs, it has been reported that SAA may not be a more specific marker for systemic inflammation (Michelle *et al.* 2014). In canine pyometra, inflammation is mainly concerned with uterine endometrium only. Hence, there was no significant change in the SAA concentration of the affected animals.

### Histological observation

#### Ovary

Ovaries in 80% of cases didn't show any prominent corpus luteum. A small cystic corpus luteum was found in the cortex of the ovaries. There was an enormous number of cystic follicles found in the ovarian cortex of all the cases. The presence of small luteal cysts with enormous follicular cysts (Fig 3) suggested the priming of a progesterone-dominated uterus with estrogen. These observations were similar to those reported by Fayrer-Hosken *et al.* (1992) and Blendinger *et al.* (1997) in bitches.

#### Uterus

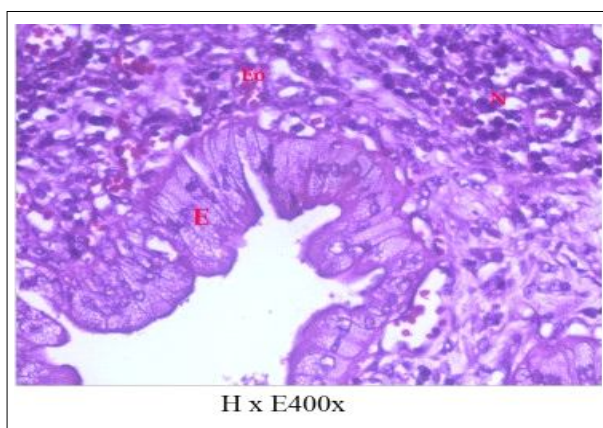
Grossly, the uterus was distended with mucopurulent to sanguinous fluid. The lumen of the uterus showed the presence of hemorrhages with the thickening of the uterine wall. Histologically the uterus showed changes in the blood supply and an increase in the thickness of the uterine glands. Massive infiltration of leucocytes, predominantly neutrophils and in such cases the lumen of the glands was distended with cellular debris, neutrophils and eosinophilic purulent exudates. These changes were manifested in the acute phase of the CEH. Along with this, uterine and glandular epithelium showed inflammatory changes and extravascular erythrocyte infiltration was observed (Fig 4). The infiltration of inflammatory cells into the endometrium has been reported by several authors (Kida *et al.*, 2010; Arora 2006).

**Table 2:** Concentration of hormonal (mean±S.E) and acute phase proteins (mean±S.E) in control and pyometra affected bitches (preoperatively and post operatively).

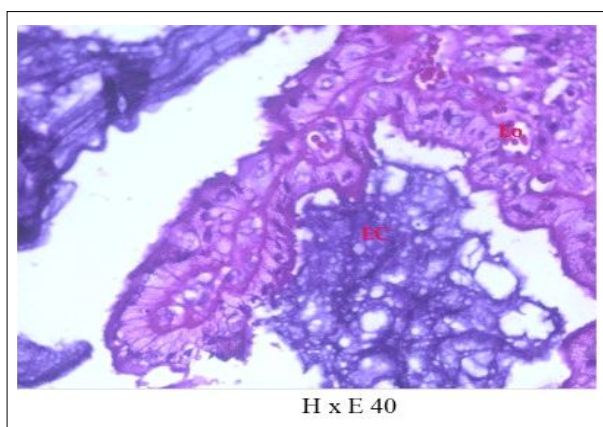
Parameters	Control	Preoperative	Day of surgery	7 <sup>th</sup> day postoperative	14 <sup>th</sup> day postoperative	F value
Progesterone (ng/ml)	0.612±0.06 <sup>a</sup>	9.77±2.64 <sup>b</sup>	8.16±2.44 <sup>b</sup>	0.09±0.02 <sup>a</sup>	0.07±0.01 <sup>a</sup>	8.917 <sup>**</sup>
Estrogen (pg/ml)	549.35±70.09 <sup>a</sup>	414.63±62.88 <sup>a</sup>	407.82±105.12 <sup>a</sup>	390.6±54.27 <sup>a</sup>	346.89±54.20 <sup>a</sup>	1.115 <sup>NS</sup>
C-Reactive protein (mg/l)	3.00±0.00 <sup>b</sup>	71.40±39.83 <sup>a</sup>	91.80±40.39 <sup>a</sup>	81.60±50.40 <sup>a</sup>	7.80±1.80 <sup>ab</sup>	1.559 <sup>NS</sup>
Serum amyloid A (ng/ml)	6.56±0.244 <sup>a</sup>	5.29±0.58 <sup>a</sup>	4.95±0.47 <sup>a</sup>	5.17±0.41 <sup>a</sup>	5.78±0.70 <sup>a</sup>	0.206 <sup>NS</sup>

<sup>\*\*</sup>Significant at 1% level ( $P<0.01$ ); <sup>\*</sup>Significant at 5% level ( $P<0.05$ ); NS not significant ( $P>0.05$ ).





**Fig 4:** Photomicrograph of uterus of pyometra bitch showing hyperplasia and ulcerative changes in the endometrial epithelium (E) and lamina propria showing degenerated neutrophils (N) and extravascular erythrocytes infiltration (E).



**Fig 5:** Photomicrograph of uterus of pyometra bitch showing endometrial cysts with tissue debris and extravascular erythrocytes infiltration (Eo).

Endometrial cysts were observed in the uterus filled with degenerated neutrophils, tissue debris and extravascular erythrocytes infiltration (Fig 5). The lining epithelium was columnar in shape with vacuolated cytoplasm. The nucleus was round and located on the base with dispersed chromatin. Similar findings were reported by Arunima (2013). Inflammation of the uterus was found in all the cases.

## CONCLUSION

Progesterone is the major contributory factor for pyometra. An extragonadal source of estrogen may be present as after ovariohysterectomy the levels of estrogen did not decline till 14<sup>th</sup> day post-operatively. Acute phase proteins showed altered variations non-significantly. The knowledge about the morphological changes and proliferation of endometrial cells during the diestrus phase in bitches is important to better comprehend the physiology and endocrinology of canines. Thus, it can be concluded that ovariohysterectomy is the treatment of choice and exploring the mechanism of

hormones and acute phase proteins will further aid in devising the reproductive biotechnologies and indicate the best moment to manipulate these female animals.

## ACKNOWLEDGMENT

The authors are grateful to the director of clinics of Madras Veterinary College for helping me conduct my research.

## Conflict of interest

All authors declare that they have no conflict of interest.

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