RESEARCH ARTICLE

Study on Incidence of Metabolic Complications due to Chronic Progesterone Exposure in Canine Pyometra

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Abstract

This study was conducted on 20 intact bitches between 2-6 years of age presented to the Veterinary Clinical Complex of the College, Tirunelveli, with the history of anorexia, abdominal enlargement, polyuria and polydipsia. After detailed anamnesis, gynaeco-clinical examination and ultrasonography all animals were diagnosed as having pyometra. Further, bitches were subjected to detailed haemato-biochemical analysis, urine analysis and intravenous glucose tolerance test. The haematological disorders encountered were anaemia, haemoconcentration, leucocytosis, thrombocytopenia, neutrophilia and monocytosis. Blood glucose tolerance values recorded were 95.92 ± 0.39 and 285.0 ± 0.72 mg/dL, respectively, at 0 and 60 min of i/v test. Higher serum values of BUN, creatinine, ALT, AST, GGT, ALP, triglyceride, cholesterol, LDH were recorded in majority of cases. These parameters were used as the diagnostic indicators for the incidence of metabolic complications in pyometra such as hepatocellular dysfunction, diabetes mellitus, nephropathy, hyperlipidemia and lactoacidosis, which was recorded in 90, 60, 70, 40 & 50% of affected dogs, respectively. Thus, this study documents the incidence rate of concealed metabolic complications arising mainly due to chronic progesterone exposure in canine pyometra and novel use of haemato-biochemical diagnostic markers to predict the prognosis and recovery rate in canine pyometra.

Key words: Canine pyometra, Complications, Diabetes mellitus, Hepatocellular dysfunction, Hyperglycemia, Hyperlipidemia.

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Introduction

Pyometra, literally meaning ''pus-filled uterus'', a common illness in adult intact middle-aged to older bitches characterized by an acute or chronic suppurative bacterial infection of the uterus with the accumulation of inflammatory exudate in the uterine lumen developing in the luteal phase during which progesterone plays a key role for the establishment of infection with ascending opportunistic bacteria (Hagman, 2022). Among the various pathological reproductive disorders in bitches, the incidence of cystic endometrial hyperplasia pyometra complex accounts for 27.27 % and is considered the major cause of canine infertility (Deka, 2003). As per Egenvall *et al.* (2005) canine pyometra is the most common diestral disorder affecting 25% of intact nulliparous bitches before 10 years of age.

Many researchers suggested that the potentially life-threatening complications of pyometra are due to prolonged progesterone exposure which leads to peritonitis, systemic inflammatory response syndrome (SIRS), hepatic dysfunction, diabetes mellitus, hyperlipidaemia, lactoacidosis and nephropathy (Samantha *et al.,* 2018; Hagman, 2022). The prognosis of pyometra depends on timely diagnosis and concomitant treatment for these metabolic complications. Thus, this study was carried out to document the incidence of various metabolic diseases occurring as a consequence to prolonged progesterone exposure in canine pyometra.

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Materials and Methods

The study was carried out on 20 intact bitches between 2 and 6 years of age presented to the SAC-OP-OG unit of Veterinary Clinical Complex, Veterinary College and Research Institute, Tirunelveli (8.7139° N, 77.7567 ° E), India, during the period from November 2023 to June 2024 with the history of anorexia, abdominal enlargement, polyuria and polydipsia. After detailed anamnesis and gynaeco-clinical examination, all animals were screened using B-mode real-time ultrasound scanner (Neroscan B1 PRO, Konica Minolta, India) with a 5-MHz transabdominal curvilinear probe to evaluate the

presence of exudate, sacculation and cystic hyperplasia of endometrial glands as per the procedures described by Nyland and Mattoon (2002). Incidence of pyometra in relevance to ultrasonographic grading of pyometra uterus as group A, B, C, D was done according to Bigliardi *et al.* (2004).

Blood samples were collected and subjected to haematological (Automated haematology analyzer, Mindray BC2800 Mindray Medical India Pvt. Ltd.) and biochemical (Automated biochemical analyzer, Biosystem A15, Biosystem Pvt. Ltd.) and electrolytes (Automated electrolyte analyzer, Sensacore ST-200, Sensa Core Medical Instrumentation Pvt. Ltd.) examinations which included parameters such as haemoglobin, PCV, TLC, DLC, TEC, platelet count, glucose, BUN, creatinine, ALT, AST, ALP, total protein, albumin, total bilirubin, triglycerides, cholesterol, lactate, LDH, calcium, phosphorus, potassium and chlorine in order to access the metabolic homeostasis in bitches affected with pyometra.

Further, animals were subjected to intravenous glucose tolerance test which involved placing a catheter in each right and left cephalic vein for glucose determinations and glucose infusion, respectively. After baseline blood sampling for glucose determination, dextrose 25% solution @ 2 mL/kg was administered through glucose infusion catheter (Poppl *et al.,* 2021). The catheter for blood sampling was flushed with normal saline and blood samples for glucose determination were collected at 3, 5, 7, 15, 30, 45 and 60 min after glucose infusion. According to procedures described by Powel (2019) urine was collected by blind transurethral urinary bladder catheterization and subjected to urinary protein, urinary creatinine and urinary GGT estimations (Automated biochemical analyzer, Biosystem A15, Biosystem Pvt. Ltd).

The data generated was tabulated and subjected to Windows Microsoft Office Excel 2021 statistical software package for mean statistical analysis.

Results and Discussion

Signalment

In the present study, the highest incidence of pyometra was observed in mesocephalic breeds followed by dolichocephalic and brachycephalic breeds (Table 1). Similar breed predisposition for canine pyometra was observed by Bhat *et al.* (2018) and Juneja *et al.* (2021). This breed predisposition in our study might be due to true genetic differences or a reflection of the different life spans in various breeds (Bhat *et al*., 2018).

Table. 1: Breed predisposition of pyometra (n=20)

Breeds of animal	Type of breed	Incidence	
		Number affected	%
Spitz	Meso-cephalic	11	55.00
Golden retriever			
Bullykutta			
Rajapalayam			
Indian ND dogs			
Doberman pinscher	Dolicho-cephalic	5	25.00
Dachshund			
Chippiparai			
Kanni dog			
Pug	Brachy-cephalic	4	20.00
Boxers			
Rottweiler			

Further, the incidence of pyometra was significantly higher in geriatric dogs (60% in < 7 years old, 35% in 5-7 years old and 15% in <5 years of age), which is in concurrence with the findings of Dabhi (2005). The high risk of pyometra in geriatric dogs might be related to the functional obsolescence of endocrine glands and increasing endometrial alterations (Hadiya *et al.,* 2021).

Clinical History

In this study anorexia was the most common clinical sign noticed followed by vomiting, abdominal distension, polydipsia and polyuria (Table 2). Similar occurrence of clinical signs was observed by Jitpean *et al.* (2017), Contri *et al.* (2015) and Liao *et al.* (2020), which might be due to the metabolic interferences of canine pyometra (Hagman, 2022).

Table. 2: Clinical signs exhibited by bitches with canine pyometra (n=20)

Clinical signs	Number of animals	Incidence (%)
Anorexia	18	90.0
Vomiting	16	80.0
Polyuria	8	40.0
Polydipsia	8	40.0
Abdominal Distension	10	50.0
Presence of vaginal discharge	12	60.0
Absence of vaginal discharge	8	40.0

The mean vital parameters in the pyometra affected animals were found to be higher than the physiological range (Table 3), which could be associated with uterine inflammation and secondary bacterial infection as well as septicaemia or bacteraemia (Fransson, 2003). The present findings corroborated with Hagman (2004) and Juneja *et al.* (2021).

Table. 3: Altered physiological vitals of pyometra bitches (n=20)

Vitals	Mean results	Inference	Incidence (%)
Rectal temperature (°C)	40.2 ± 1.6	Pyrexia	70.0
Heart rate (bpm)	88.4 ± 4.8	Tachycardia	50.0
Respiration rate (/min)	32.6 ± 3.2	Tachypnoea	50.0

During this study, vaginal discharge was observed in 12 bitches (60%), but was absent in 8 cases (40 %), which reveals that the incidence of open cervix pyometra was higher than closed cervix pyometra. Further, the incidence of

purulent discharge was higher in present study (41.6%, 5/12), followed by serosanguinous (33.3%, 4/12), and haemorrhagic (25.0%, 3/12) discharge. These findings were in concurrence with Feldman and Nelson (2004), who stated that the most common clinical finding in bitches with open cervix pyometra is malodorous vaginal discharge, which is dependent on the patency of the cervix and the nature of vaginal discharge, which depends on the type of invading microorganism.

Ultrasonographic Examination

In this study the mean endometrial thickness in open cervix pyometra was higher than in closed cervix pyometra (3.75±0.15 Vs. 2.98±0.15 mm), however uterine sacculations size were found smaller in open cervix pyometra (0.68±0.18 Vs. 1.89±0.45 cm), which was in agreement with the findings of Samantha *et al.* (2018). This decreased uterine thickness in closed cervix pyometra could be due to increased rate of toxic metabolite perfusion across the uterine wall, while the evacuation of uterine contents accounts for decreased sacculation size in open cervix pyometra (Egenvall *et al.,* 2005).

In this study the incidence of group C (many and large cysts, irregular surface and hypertrophic endometrium) and group D (many and large cysts in all the uterus, irregular surface and hypertrophic or atrophic endometrium, hyperechoic uterine content) pyometra was 30% (6/20) and 35% (7/20), respectively, while that of group A (no cysts, normal endometrial surface and anechoic uterine content) and B (few and small cysts, normal endometrial surface, anechoic uterine content) was 15% (3/20) and 25% (5/20), respectively, which coordinated with the findings of Samantha *et al.* (2018). Further, Bigliardi *et al.* (2004) and Hagman (2022) also recorded higher severity of clinical signs exhibited by Group D pyometra as compared to other groups.

Haematology

During this study, the major haematological disorders encountered were anaemia, haemoconcentration, leucocytosis, thrombocytopenia, neutrophilia and monocytosis (Table 4). Similar occurrences were documented by Hagman (2004), Samantha *et al.* (2018), Contri *et al.* (2015) and Juneja *et al.* (2021). However, the lymphocyte count in this study was contrary with the findings of Gandotra *et al.* (1994), who suggested lymphopenia in pyometra bitches.

The possible reasons for the development of anaemia and haemoconcentration in this study are endotoxic depression of bone marrow or suppression of the reticuloendothelial system by circulating hormonal metabolites or lack or erythropoietin stimulus from metabolically affected kidneys in bitches affected with pyometra or haemostatic impairment by circulating endotoxins (Tanja *et al.,* 2006). The occurrence of thrombocytopenia in this study might be attributed to the endotoxin mediated platelet activation and aggregation with fibrin in order to act as chemokine attractants thus decreasing the circulatory thrombocytes (Boyer and Habib, 2005). The marked leucocytosis and neutrophilia observed in cases of pyometra is suggested to be due to bone marrow inflammatory response to combat diffused suppurative inflammation of uterus (Sevelius *et al.*, 1990). Monocytosis recorded in this study could be attributed to chronic inflammatory response from the uterus (Samantha *et al.,* 2018).

Biochemical Profile

***Hepatocellular dysfunction*:** This study documents that 90% of pyometra bitches were affected concurrently by hepatocellular dysfunction characterized by higher serum values of BUN (38.92±0.89 mg/dL), creatinine (2.3±0.12 mg/dL), ALT (168±5.93117±4.85 IU/dL), AST (91.85±5.20 IU/dL), GGT (12.29 ±0.26 IU/dL) and ALP (IU/dL), which might be attributed to circulating progesterone metabolites induced inhibition of the Farnesoid X receptors in the liver resulting in hampered bile homeostasis and hepatic injury which is further aggravated by bacterial endotoxin mediated hepatic damage. These findings are in agreement with Singh *et al.* (2019).

Table. 4: Haematological findings in pyometra bitches (n=20)

Haematological parameters	Mean results	Inference	Incidence (%)
Haemoglobin (g/dL)	7.29 ± 0.34	Anaemia	85 (n=17)
Total RBC count (10^6/µL)	5.18 ± 0.13		
PCV (%)	52.92 ± 1.41	Haemoconcentration	75 (n=15)
Total WBC count (10^3/µL)	27.82 ± 11.39	Leucocytosis	60 (n=12)
Platelet count (10^5/µL)	1.98 ± 0.16	Thrombocytopenia	75 (n=15)
Neutrophil (%)	84.6 ± 5.33	Neutrophilia	75 (n=15)
Lymphocyte (%)	18.5 ± 4.74	Normal reference range	100 (n=20)
Eosinophils (%)	1.2 ± 1.54	Normal reference range	100 (n=20)
Basophils (%)	1.1 ± 2.54	Normal reference range	100 (n=20)
Monocyte (%)	3.6 ± 0.84	Monocytosis	75 (n=15)

Diabetes mellitus: During this study occurrence of hyperglycemia in pyometra bitches was 60% (12/20) through intravenous glucose tolerance (Blood glucose 95.92±0.39 and 285.0±0.72 mg/dL at 0 and 60 min), which might be due to progesterone-mediated reduction in insulin binding affinity to the high-affinity and low-capacity insulin receptors and inability to compensate for this reduced affinity by an increase in total binding capacity (Poppl *et al.,* 2021). Similar findings were also recorded by Kim *et al.* (2019) and Poppl *et al.* (2021).

Hyperlipidemia: The incidence of hyperlipidaemia in pyometra bitches in this study was 40% (8/20) characterized by elevated triglyceride (168.15±0.89 mg/dL) and cholesterol (440.15±10.79 mg/dL). These findings are in agreement with Cheluvappa *et al.* (2010). This hyperlipidemia in pyometra bitches might be due to sepsis-induced lipoprotein lipase inhibition and upregulated hepatic triglyceride production due to progesterone-mediated intrahepatic cholestasis (Hayyeh and Williamson, 2015).

Lactoacidosis: The incidence of lactoacidosis in canine pyometra was 50% (10/20) characterized by elevated serum LDH (1066.15±34.69 mmol/dL) and Lactate (76.17±3.34 mg/dL). This is in concurrence with Volpato *et al.* (2012). The occurrence of lactoacidosis might be associated to the oxidative stress resulting in tissue hypoxia by compensated lactate shuttle phenomenon (Suetrong and Walley, 2015).

Nephropathy: In this study the incidence of nephropathy was 70% (14/20) characterized by elevated urinary creatinine: UGGT ratio (174±0.58) and urinary protein (9.6±1.45 mg/dL), which concurred with the findings of Gupta *et al.* (2019), Poppl *et al.* (2021) and Andrade *et al.* (2023). This nephropathy might be due to loss of urine-concentrating ability by the kidney secondary to bacterial endotoxin induced renal tubular impairment and chronic exposure to hyperglycemic body fluid in canine pyometra (Figueiredo *et al.,* 2017).

Conclusion

This study concluded that the incidence of hepatocellular dysfunction followed by nephropathy and diabetes mellitus was high in canine pyometra. Further, these life-threatening complications during pyometra might be due to prolonged progesterone exposure and uterine endotoxin seepage which act as major determinants of prognosis and recovery from canine pyometra. Hence, timely diagnosis of these metabolic complications and concurrent therapeutic management hastens the recovery from canine pyometra.

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