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Reproductive Disorders in Companion Animals: A Review

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ABSTRACT

The diseases of different female genital organs in companion animals possibly will affect the health condition of the animal, fertility status, or even the life of the animal. There may be an aberrant reproductive cycle of dogs and cats if there is a lesion in the genital tract. The frequent reproductive disorders seen in companion animals are ovarian, uterine and vaginal in origin. The majority of the animals are suffering from ovarian diseases commonly cystic ovaries, ovarian remnant syndrome and ovarian tumors. Certain reproductive disorders *viz*., pyometra, cystic endometrial hyperplasia and metritis, might cause infertility in the bitch and queen as well as lead to the death of the animals, if not diagnosed and treated in the early hours. Vaginal, cervical prolapse and vaginal tumors are very frequent in bitches and rare in cats. The transmissible venereal tumor (TVT) is an exclusive tumor that mostly affected by the dogs. Pseudo-pregnancy is familiar in dogs but uncommon in cats.

Key words: Cat, Dog, Reproductive disorders.

Reproductive disorders are usually seen in small animal practice. The regular reproductive ability of dogs and cats may be gravely influenced if there is a lesion in the ovaries, uterus and vagina and may put the common health of the animals at risk. The cystic lesions of the bitches and queens' uterus might be associated with the uterine serosa, myometrium or endometrium and encompass of serosal inclusion cysts, adenomyosis, endometrial polyps, cystic remnants of mesonephric ducts and cystic endometrial hyperplasia (Schlafer and Gifford, 2008). The clinical signs will possibly vary, but genital disease often presents with various degrees of lethargy, anorexia, swelling of the affected area and, in females, vaginal discharge can be observed with a series of ovarian and uterine affections. In that case, abdominal ultrasonography can be very helpful in cases of genital diseases. Abdominal radiography can also be helpful, although can be less sensitive than ultrasound. Boro *et al.* (2019) reported that the overall prevalence rate of reproductive disorders in dogs and cats was 8.15% (dog 7.48%, cat 0.66%). The highest percentage was recorded in the month of August *i.e*. 13.51% (Boro *et al.,* 2019). The different causes of reproductive disorders in dogs were delayed puberty (4.05%), dystocia (16.16%), Azoospermia (2.70%), mis-mating (8.05%), posthitis (4.05%), pseudopregnancy (5.40%), abortion (2.70%), fetal maceration (1.35%), open pyometra (12.16%), close pyometra (9.45%), post partummetritis (9.45%), decreased libido (1.35%), orchitis (4.05%), vaginal prolapsed (2.70%), uterine inertia (1.35%), balanoposthitis (2.70%), vaginal lipoma (1.35%), transmissible veneral granuloma (1.35%), fetal mummification (1.35%). In cats the reproductive disorders were dystocia (5.40%) and abortion (2.70%) (Boro *et al.,* 2019). Various commonly encountered reproductive diseases in companion animals are briefly discussed as follow:

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Pyometra

Pyometra is a pathological situation of the affected uterus of middle-aged to old, diestrous bitches and possibly will occur as a result of an overstated and abnormal response to chronic and repeated progesterone spur (Corrada *et al*., 2006; Haji *et al*., 2018). There is an incursion of *Escherichia coli* (*E. coli*) into the uterus from the vagina and it starts to multiply within the numerous cysts and crypts when the local immunity is compromised and it might lead to local tissue degeneration and the development of pyometra (Batista *et al*., 2016). A bitch havinga history of recent estrus and typical clinical signs of polyurea, polydipsia, vaginal discharge, should be under suspicion. In certain condition, there may be a lack of vaginal discharge in bitches (Fig 1 A) in where the diagnosis can be more challenging. Haemato-biochemical findings in affected animals with pyometra are not specific for pyometra and often reveal inflammation and secondary metabolic instability. The consequences of a complete blood count often demonstrate neutrophilia with a regenerative left shift; on the other hand, a normal white blood cell count or even neutropenia with a degenerative left shift might be identified in animals with

endotoxemia (Hardy and Osborne, 1974). There might be dehydration of the animal which often contributes to elevated BUN and creatinine concentrations, although simultaneous kidney insufficiency in an older bitch mayalso be responsible for the azotemia (Asheim, 1965). The kidney damage which is secondary to immune complex deposition, has not been provided with evidence in current studies (Heiene *et al*., 2007). Abdominal ultrasonography (Fig 1B) is the most favored method for diagnosis of pyometra in bitches and queen (Dennis and Brian, 2012). In a case with uterine rupture, free fluid might be observed inside the abdominal cavity and the omentummight be hyperechoic secondary to bacterial peritonitis. Abdominal ultrasonography can also be used to rule out other conditions that can cause uterine extension or vaginal discharge, such as early pregnancy (Dennis and Brian, 2012; Haji *et al*., 2017).

Cystic endometrial hyperplasia (CEH) is a pathological condition of compromised uterus of middle-age to old diestrous female dogs as a result of an abnormal response to chronic and repeated progesterone stimulation (Corrada *et al*., 2006). From vagina, *E. coli* enters uterus and begins to proliferate inside cysts and crypts leading to the development of pyometra, hence, the condition known as CEH-pyometra complex (Batista *et al.,* 2016). The medical treatment of this condition involves repeated administration of a prostaglandin either alone or in combination with a prolactin inhibitor (Baithalu *et al*., 2010). In addition, the use of methyl ergometrine helps to potentiate the stimulatory effects of prostaglandins and reduces their total dose (Haji *et al*., 2017).

Foetal mummification and maceration

Pregnancy loss is generally divided into embryonic and foetal death (Konwar *et al.*, 2020). Foetal death is impulsive

A. Whitish discharge in pyometra affected bitch.
B. Ultrasonographic imaging of pyometric uterus with irregular thickening of the uterine wall and distended uterus (Talukdar *et al*., 2022 a).
C. Mummified fetuses of dog (Devi *et al*., 2020).
D. Ultrasonographic imaging of the pregnant uterus of a bitch showing a mummified fetal skull.
E. Macerated fetuses of a dog.
F. Abdominal ultrasonographic examination revealed the distension of the feline uterus with no viable fetuses (Talukdar *et al*., 2022 b).

Fig 1: Reproductive diseases of companion animals.

and predisposed by numerous factors and mummification is one of the possible outcomes. Though foetal mummification has been recorded in dogs, its occurrence is assumed to be very low (Lefebvre, 2015). Foetal mummification does not take place in the first half of the pregnancy as embryonic or foetal death before growth of the foetal bones generally leads toresorption (Johnston *et al*., 2001 and Lorenz *et al*., 2009). Foetal death happening in the late gestation, not linked with abortion or maceration, might be followed by foetal mummification. Foetal mummification is a sterile state due tomorphological changes of the retained dead fetus subsequent tothe first half of the pregnancy, in the presence of a mature foetal skin resistant to autolysis (Grunert *et al*., 2005; Linde-Forsberg, 2010). Foetal mummification normally occurred after ossification of foetal bones, if there is no bacterial infection parallel with or causing death of the foetus (Robinson *et al*., 2003). The uterus contracts on the foetus, the placental fluids are absorbed and the foetal membranes become shrivelled and dried (Roberts *et al.,* 2004), resembling parchment (Arthur *et al.,* 2001). Foetal mummification has been reported in numerous species but is more common in cattle; uncommon and sporadic in canines (Roberts *et al*., 2004) and common in polytocous and rare in monotocous species (Perumal and Srivastava, 2011).

Fetal maceration is associated with fetal death (Fig 1C and D) and incomplete abortion to occur as a consequence of uterine inertia and intrauterine infections (Devi *et al.,* 2020). The most common cause is infection when, bacteria go through the uterus *via* the cervix after the foetus's death, causing putrefaction and autolysis of the soft tissues and sending offfoetal bones within the uterus (Long, 2009). Following bacterial contamination, fetal emphysema develops within 24-48 hours and maceration occurs within 3-4 days (Bhattacharyya *et al*., 2015). There might be putrefication and autolysis of fetus or fetuses (Fig 1E and F) at varying degrees, depending on the pathogenicity of the bacteria. If maceration occurs after bone formation, autolysis could continue until all fetal soft tissues are autolysed, leaving only bones (Drost *et al*., 2007). The bone fragments that remain inside the uterus could be well-established in the uterine wall (Noakes, 2009), which causes chronic endometritis or severe damage to the endometrium. As reported earlier, the occurrence is quite low in bitches (Mahla *et al*., 2016). On the other hand, most cases, there are no symptoms in the mother, leading to misdiagnosis (Gill, 2001).

Uterine inertia

Uterine inertia is a situation of unproductive labour. It is a common cause of dystocia in bitch (Noakes, 2009) and it is classified as primary (*i.e*., no uterine contractions) or secondary (*i.e*., initially uterine contraction, later on ceases due to muscular exhaustion). Dystocia in cats is typically due to maternal causes (67%), with uterine inertia as the primary cause in about 60.6% of cases (Borpujari *et al*., 2019). The sensitive cells in the cervix and vagina transmit nerve impulses to neurons in the hypothalamus, which in turn trigger the release of oxytocin from the posterior pituitary gland, leading to increased myometrial contractions (Ferguson, 1941). In certain mammal species oxytocin is produced in the uterus and the foetal membranes as well (Chibbar *et al*., 1993). The primary uterine inertia, which can be further, classified as complete or incomplete (Borpujari *et al*., 2019). In case of complete uterine inertia, not a single puppy is delivered because of apparent uterine muscle fatigue. However, incomplete inertia occurs when there is normal delivery of a litter on the other hand, the uterus fatigues before parturition is completed (Johnston *et al.,* 2001). Oxytocin and calcium gluconate are the most commonly used medicine in uterine inertia in bitch. Oxytocin helps in the contraction of the uterine musculature (Chutia *et al*., 2016).

Cervico-vaginal prolapse

Cervico-vaginal prolapse (Fig 2C) is an uncommon situation in bitch when compared to other vaginal pathologies like vaginal tumours or urethral tumours, which protrude into the vagina and obstruct the canal (Konig *et al*., 2004). The young bitches preferably less than 2 to 3 years age are mostly susceptible to vaginal prolapse (Talukdar *et al*., 2019). It can be linked with the whelping during prolonged labor or upto 48 h after parturition (Arthur *et al*., 1996) which possibly due to excessive relaxation and stretching of the pelvic muscle (Benesch and Wright, 2001), parallel vigorous tenesmus and uterine disease, coarse handling during delivery, genetic predilection and abnormal connective tissue (CT) metabolism (Ozyurtlu and Kaya, 2005). Generally, it was observed near parturition, as the serum progesterone concentration decreased and the serum estrogen concentration increased close to whelping (Rani *et al*., 2004). The incidence is less during diestrus, anestrus and normal pregnancy (Johnston, 1989). At the time ofprolapse, there might be edematous swelling of the vaginal mucosa, which is accompanied by increased vaginal hyperemia and oedema due to high serum estrogen levels (Johnston *et al*., 2001) during proestrus and estrus (Schaefers-Okkens, 2001). The strengthening of a high serum estrogenic response can lead to disproportionate mucosal folding of the vaginal floor just cranial to the opening of the urethra, which finally results in protrusion of vaginal mucosa from the vulva (Talukdar *et al*., 2019). In chronic cases, the protruded mucosa is usually necrosed and inflamed usually necrosed and inflamed and can rupture easily (Kumar *et al.,* 2011).

Dystocia

Dystocia (difficult birth) occurs when the first or second stage of labour is prolonged and assistance is necessary for delivery (Noakes, 2009) (Fig 2 A and B). It is of either fetal origin or maternal origin or both. In cats, dystocia frequently occurs due to maternal causes (67%), out of which uterine inertia, being the major cause, occurs in about 60.6% of cases as reported by Ekstrand and Linde

Forsberg (1994). In dog, maternal dystocia is also common (60% to 75.3%) as described by Darvelid and Linde-Forsberg (1994) and Boro *et al*. (2019). Ekstrand and Linde -Forsberg (1994) reported that the most frequent cause of maternal dystocia is uterine inertia, accounting for 40% to 72% of all dystocia reported to the dam. Uterine inertia is the failure to expel a fetus from the uterus when no obstruction exists (Ekstrand and Linde-Forsberg, 1994). Complete primary uterine inertia is observed when the second stage of labour fails to establish and puppies are yet to be delivered. Partial primary uterine inertia is defined as the commencement of normal labour but failure to deliver all puppies (Gendler *et al.,* 2007). Generally primary uterine inertia develops when the litter size is too small, or the myometrium is overstretched secondary to a large litter size. More than 50% of casesin bitches with complete primary inertia had three or fewer pups in their litter (Ekstrand and Linde-Forsberg, 1994). Primary uterine inertia is also attributed to inherited predispositions, nutritional or neuroendocrine imbalance, age-related changes, nervous inhibition and systemic disease (Wykes and Olson, 2003). Secondary uterine inertia is the exhaustion of the uterine musculature subsequent to contracting against an obstruction and has been reported to occur in 3.2% to 12.6% of total dystocia (Gaudet, 1985). The obstructions might be from the maternal side or because of a narrow pelvis, congenital malformation, pelvic trauma, neoplasia or abscess, vaginal stricture, uterine torsion, uterine or vaginal prolapse and vaginal hyperplasia (Linde-Forsberg and Eneroth, 2000). Darvelid and Linde-Forsberg (1994) reported that fetal anatomic and orientation changes accounted for most of the cases of fetal dystocia reviewed (24.7% to 40%). Oversized (6.6 to 13.7%), malformed (1.6%), or mispresented (15.4 to 15.8%) fetuses can cause dystocia, as can dead (1.1%) or glucocorticoid-deficient fetuses (Darvelid and Linde-Forsberg, 1994). Puppies are delivered in anterior presentation in 60% of cases; however, there is no association between dystocia and delivery position (Van der Weyden *et al.,* 1981). Eneroth *et al*. (1999) reported that a mixing of maternal and fetal

A. Dystocia in bitch.
B. Dystocia in cat.
C. Cervico-vaginal prolapse in a bitch (Talukdar *et al*., 2019).
D. Male Pseudohermaphroditism in a bitch (Alam *et al*., 2007).
E. Vaginal Leiomyoma in bitches (Saikia *et al*., 2018).
F. Canine transmissible venereal tumour.

Fig 2: Reproductive disorders of canine and feline.

factors might lead to the development of dystocia. Various dog breeds are associated with an increased risk of dystocia. Scottish terriers and Boston terriers have inherited characteristics that predispose them to obstructive dystocia (Eneroth *et al*., 1999). It has been said that the secondary uterine inertia occurs in Scottish terrier bitches due todorso-ventral pelvic flattening and smaller vertical pelvic canal diameter (Eneroth *et al*., 1999). Boston terriers have analogous pelvic measurements, but fetal oversizing is a causal factor to obstruction (Eneroth *et al*., 1999). Another study by Darvelid and Linde-Forsberg (1994) on 182 dystocia cases in Sweden did not find a significant breed disposition. Although some dog breeds have genetic predispositions to dystocia, breed identification has been inadequate due to local breed popularity and investigators' failure to obtain a representative sample of the dystocia patient population.

Intersex

Intersex animals are either pseudohermaphrodites or hermaphrodites based on their gonads (Howard and Bjorling, 1989). True hermaphrodites have the gonadal tissue of both sexes while pseudohermaphrodites (Fig 2D) have the gonads of one sex but the secondary sex characteristics and external genitalia of the opposite sex. The male pseudohermaphrodites have testes while there are diverse or female external genitalia. In the case of true hermaphroditism, both testicular and ovarian tissues are present in different proportions. A testis may be found on one side in mixture with an ovary on the contralateral side, an ovotestis only may be present, or an ovotestis may be paired with a testis or ovary (Saikia *et al*., 2017). These developmental disorders are caused by abnormalities of genetic or chromosomal origin,or inappropriate hormonal or chemical contact (Passello-Legrand and Mowat, 2004). In mammals, reproductive development disorders have been described in several species including humans, pigs, goats, horses and dogs (Cribiu and Chaffaux, 1990; Kim and Distl, 2006). The word hermaphrodite is normally used independently of the chromosomal constitution. They might have an ovary on one side and a testis on the other or they may have a collective of ovotestes (Kai *et al*., 2003). A pseudohermaphrodite has deviation between phenotypic and gonadal sex (Del Amo *et al*., 2001). Kennedy and Miller (1993) said that male or female pseudo hermaphrodite were categorized on the basis of single type of germinal tissue present in the body.

Neoplasia

In bitch neoplasia is more frequent in the lower reproductive tract *i.e*. vagina and vulva, as compare to uterus and ovaries (Saikia *et al*., 2018). Tumors of the tubular genital tract of females occurred 3% of total canine tumors and out of which 85-90% found in the vulva, vagina and vestibule (James *et al*., 2012). Frequent found canine vaginal or vulvar neoplasms are leiomyoma (Fig 2E), leiomyosarcoma, fibroma and transmissible venereal tumor (MacLachlan and Kennedy, 2002) and leiomyoma is a main tumor of smooth muscle cells that may take place in any organ with a connective tissue or mesenchymal part and have been found in female genital tract (James *et al*., 2012; Singh *et al*., 2014). The medium aged non-spayed dogs suffer more (Koestner and Higgins, 2008). Vaginal leiomyomas may be single or multiple, intraluminal or extraluminal and usually round or oval, well-defined and encapsulated. The size and consistency may differ depending on the length of growth, becoming firmer as connective tissue increases. The large intraluminal tumors may stick out through the vulva, while extraluminal tumors have a predisposition to cause perineal swelling (Umamageswari *et al.,* 2016). In connection to leiomyomas of the genital tract, the estrogen secreting tumors or ovarian follicular cysts are alsoreported.

Canine transmissible venereal tumour

Hujard was the scientist who first described the canine transmissible venereal tumour (TVT) also known as Sticker's sarcoma, in Europe in 1820 and it was said that his name was linked to Sticker. It is also known as venereal granuloma, infectious sarcoma or transmissible lymphosarcoma a benign reticuloendothelial tumour of the dog frequently affects the external genitalia (Fig 2F) and intermittently the internal genitalia (Tella *et al.,* 2004). It is transmitted mostly by sexual contact and possibly by direct contact related to the social behaviour of the dog like sniffing, licking of the genitalia and bite wounds during fights. It is to be found in the external genitalia of both sexes and is barely ever found somewhere else in the body, whereas it metastasises in only a very few cases. There may be inoculation of intact neoplastic cells in the damaged mucosa or skin of the dog. It is common between 2 and 5 years of age (Higgins, 1966). In India, the prevalence of such tumour was reported as 23.5% to 42.8% (Abedin, 2020). The lesions turn pink to red and diameter is 1-3 mm; they are pedunculated or dermo-epidermal. There may be hemorrhagic, cauliflower-like friable masses. The diameter of the initial nodular mass is 5 to 7 cm and, if it invades deeper into the mucosa and forms subcutaneous lesions, it can exceed 10-15 cm (Hoque, 2002). Numerous therapeutic regimes both invasive and non-invasive such as surgery, immunotherapy, radiotherapy, biotherapy and chemotherapy are used to treat the animal with TVT. In this regard, chemotherapy has been proven to be the most effective with vincristine sulfate Vincristine can be given weekly at a dose of 0.025 mg/kg, IV (Calvet, 1982). There may be myelosuppression, gastrointestinal disorder, leukopenia and vomiting after administration of Vincristine as it is a cytostatic drug. If WBC count is below 4000 mm^3 then the drug may be administer 3 to 4 days later with the dose rate 25% below of the initial dose. Other drugs that can be used for the treatment are cyclophosphamide (5 mg/kg, PO, for 10 days or given in combination with prednisolone (3 mg/kg, for 5 days), vinblastine (0.1 mg/kg, IV during 4 to 6 weeks at weekly interval), methotrexate (0.1 mg/kg, PO, every alternate day) or all the 3 drugs can also be used as combine therapy (Abedin, 2020).

Ovarian cysts

In companion animals, the follicular cysts, luteal cysts, germinal cysts, cystic corpora lutea, cystic rete ovarii, cystic atretic follicles, cystic granulosa cell tumours and cysts of the subsurface epithelial structures have been reported as common in older animals (Johnston *et al*., 2001). The follicular cysts that developfrom mature or atretic follicles are considered the most common; however, their causes in impulsive diseases are unknown (Johnston *et al*., 2001). In veterinary practice, follicular cysts have been studied more due to the fact that these cysts are responsible for secretion of various amounts of hormone either causing anomalous clinical signs andoestrus irregularities (Johnston *et al*., 2001).

Advancements in veterinary reproductive medicine (theriogenology) have moved beyond traditional surgical spaying/neutering towards specialized diagnostics and minimally invasive, medical therapies designed to treat infertility and prevent disorders, particularly pyometra and cystic endometrial hyperplasia. Modern diagnostics enable early detection of reproductive pathologies, improving the prognosis for both breeding and non-breeding animals. High-definition ultrasonography is used for early pregnancy diagnosis (as early as 16 days in cats), fetal viability monitoring and identifying cystic endometrial hyperplasia (CEH) or pyometra. Serial serum progesterone testing is now standard for precise ovulation timing, allowing for optimal breeding and for diagnosing disorders like luteal insufficiency. Molecular diagnostics such as real-time PCR and RT-PCR are increasingly used to identify reproductive pathogens (*e.g.*, FeLV/FIV, *Brucellacanis*) and genetic screening. Routine, inexpensive monitoring of vaginal cells to determine the stage of the estrous cycle and identify inflammation or infection.

If we search the advances in therapeutic approaches, newer, alternative drug treatments allow for medical management of conditions previously treated only with surgery, with fewer side effects. The use of antiprogestins (*e.g.*, Aglepristone/Alizine) in combination with prostaglandins has shown high success in treating open pyometra, sparing the uterus for future breeding. GnRH Agonists (Implants) like long-acting deslorelin implants can induce or suppress estrus and serve as a reversible alternative to chemical castration in male dogs, though availability varies globally. Non-surgical pregnancy termination like progesterone antagonists (Aglepristone) and dopamine agonists (Cabergoline) offer safer alternatives to older estro-progestin drugs for pregnancy termination, with reduced risks of uterine complications. Improved protocols for managing dystocia (difficult labor) using oxytocin and calcium and using dopamine antagonists to treat mastitis and agalactia.

Recommendations for breeders/owners

Improved management depends on proactive education and understanding the reproductive cycle.

- **Understand the cycle:** Owners must recognize that dogs are non-seasonal monoestrous (1-3 cycles per year) and cats are seasonally polyestrous (induced ovulators).
- **Keep records:** Maintain a dedicated calendar to record the first day of vaginal discharge (proestrus), the duration of heat and the dates of breeding.
- **Proactive health checks:** For breeding, perform pre-breeding evaluations including brucellosis testing, vaginal cytology and physical examination to detect anatomical abnormalities.
- **Nutrition and weight:** Maintain a healthy weight; obesity is a leading cause of infertility and dystocia.
- **Responsible mating:** Avoid inbreeding (Mating of closely related individuals) to prevent “inbreeding depression, which reduces fertility and litter size.
- **Post-partum management:** Monitor mothers for signs of eclampsia (calcium deficiency) and puppies/kittens for consistent weight gain.

CONCLUSION

Reproductive disorders in companion animals are fairly common and can be quite distressing to the animals, especially when secondary infections are present. The most common projected affections are seen in the uterus, than the ovaries. Habitually, bitches with uterine lesions were coupled with ovarian lesions. Ultrasonography and radiography are the most useful diagnostic tools. Surgery with or without ovariohysterectomy is the treatment of choice in most of the cases. Sufficient pre, peri and post-operative care is seldom necessary in which involves supportive nutrition, adequate analgesia and antibiotic coverage.

The shift toward medical, non-surgical interventions for reproductive disorders offers hope for preserving the breeding potential of valuable pets, while advanced diagnostics allow for better management of the breeding cycle and prevention of fatal diseases like pyometra.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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