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Uterine prolapse observed during and immediately after parturition in three dogs: case report and literature review

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Abstract: Uterine prolapse (UPR) in bitches is a rare obstetric emergency. Generally, it occurs within 48 hours postpartum in bitches. Opposite this datum, in this case report three instances of UPR presented as two during parturition and one at 40 days postpartum. Besides one of them, which occurred during labor, was complicated by uterine rupture. Although no definitive etiology has been determined, it seems that the leading cause is weakness in pelvic connective tissues. Factors contributing to UPR include excessive relaxation of pelvic ligaments, difficult labor, and excessive straining. The extracellular matrix (ECM), composed mainly of collagen and elastin, is crucial in maintaining tissue integrity. Hormones like estrogen, progesterone, and relaxin significantly affect the ECM's structure during pregnancy and parturition, influencing pelvic elasticity and uterine strength. Besides, our cases showed that poor body condition, parity, age, and breed predisposition are also suspected as contributing factors. All the animals were treated by surgery. Three cases show mothers and/or puppies may survive with timely and appropriate surgery. Besides, we believe that ovariohysterectomy is the best treatment choice with both survivor and prevention effects. However, to clearly define both the primary factors and co-factors speculated by this report, further research is required to investigate.

Keywords: *Dog, Parturition, Uterine prolapse.*

Üç köpekte doğum sırasında ve hemen sonrasında görülen uterus prolapsusu: olgu sunumları ve literatür derlemesi

Özet: Köpeklerde uterus prolapsusu (UPR) nadir görülen bir obstetrik acil durumdur. Genellikle köpeklerde doğumdan sonraki 48 saat içinde meydana gelir. Bu veriye zıt olarak sunulan raporda ikisi doğum sırasında ve biri postpartum 40. günde şekillenen üç UPR olgusu bildirilmiştir. Doğum sırasında şekillenen olgulardan bir tanesi uterus rupturu ile komplike olarak gelişmiştir. Kesin bir etiyolojisi olmasa da başlıca neden pelvik bağ dokularının zayıflığı gibi görünmektedir. UPR'ye katkıda bulunan faktörler arasında pelvik bağların aşırı gevşemesi, güç doğum ve aşırı zorlanma yer alır. Esas olarak kolajen ve elastinden oluşan ekstraselüler matriks (ECM) doku bütünlüğünün korunmasında çok önemlidir. Östrojen, progesteron ve relaksin gibi hormonlar, gebelik ve doğum sırasında ECM'nin yapısını önemli ölçüde etkileyerek pelvik elastikiyetini ve uterus gücünü değiştirir. Ayrıca, olgularımız zayıf vücut kondisyonu, doğum sayısı, yaş ve cins yatkınlığının da predispoze faktörler arasında olabileceğinden şüphelendirmiştir. Tüm hayvanlar cerrahi olarak tedavi edilmiştir ve elle prolabe kitle reddenin küçük ırklarda işe yaramadığı ancak büyük ırklarda bir şans yarattığı belirlenmiştir. Üç vaka da anne ve/veya yavruların zamanında ve uygun cerrahi müdahale ile kurtarılabilmiştir. Hem sağ kalım hem de korunma açısından ovariohisterektominin en iyi tedavi seçeneği olduğu görüşüne de ulaşılmıştır. Ancak bu raporda öne sürülen hem birincil faktörleri hem de yardımcı faktörleri net bir şekilde tanımlayabilmek için daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler*: Doğum, Köpek, Uterus Prolapsusu.*

Introduction

Uterine prolapse (UPR) is an obstetrical emergency condition infrequently reported in dogs and cats (Nelissen, 2015). The urgency of these cases arises from the risk of contamination, obstruction of ovarian arteries and veins, rupture resulting in hemoperitoneum, peritonitis, dehydration, and hypothermia (Davidson, 2003). It is less common in dogs compared to cats (<0.003% vs 0.8%, respectively) (Davidson, 2003; Payan-Carreira et al., 2012). One or both uterine horns may prolapse through the dilated cervix and vulva (Nelissen, 2015) during the peripartum period (up to 48 hours postpartum) (Feldman and Nelson, 2004). There is no definitive cause of UPR but predisposing factors including excessive relaxation/stretching of the pelvic musculature, prolonged dystocia, inadequate obstetric maneuvers, oversized fetus, multiple pregnancies, uterine atony, excessive abdominal contractions, severe tenesmus, incomplete placental detachment (Binli et al., 2021; Özyurtlu and Kaya, 2005), and cystic endometrial hyperplasia (CEH) (Greiling et al., 2023). While it could be confused with vaginal prolapse and tumors (Nelissen, 2015), the diagnosis was made quickly with the medical history and visualization of a tubular mass protruding from the vulva.

In this report, three cases of UPR occurred without a history of obstetric maneuvers. Two cases (case 1 and case 2) were observed during parturition, and one of them was complicated by uterine rupture (UR) (case 1); the last one (case 3) occurred immediately postpartum and reoccurred despite being rejected several times.

Material and Methods

The animal material consisted of three dogs diagnosed with UPR in our clinic. General information on the cases is presented in Table 1.

Only non-experimental animals were used in this study. Internationally recognized high standards of individual veterinary clinical patient care were followed, and routine clinical treatment was performed. Therefore, ethical approval from a committee was not required.

Table 1. General information, examination and treatment findings of cases.

Signalements	Case 1	Case 2	Case 3
Breed	Kangal	Pekingese	French bulldog
Age (y)	4	4	1
BW (kg)	28	7	6.5
Parity	Multiparous	Multiparous	Primiparous
Prolapsed part	LUH	RUH	UB
Prolapsed time	8th h at parturition	24th h at parturition	İmmediately after parturition and continues to prolapse
Presenting to hospital	1 h later	6 h later	24 h later (after last occurrence)
Obstetric intervention	No	No	No
Previous treatment	No	No	Manually rep. x3
Physical examination	Slight dehydration	Slight dehydration	No abnormality
Inspection of mass	Bloody-green dis. PA Fetal structures Uterine rupture	Placental area. Ut. starting to dry Necrotization in PA	Bloody dis. Ut. starting to dry
Ultrasonography	Multiple fetuses Fetal viability	One fetus Fetal viability Invagination (Fig. 2B)	No fetuses No fetal structure Ut. diameter 1.5 cm
X Ray	>5 fetuses in abd.	1 fetus in abd.	No fetus in abd.
CBC	Slight anemia	In reference interval	Slight anemia
Treatment	Manually obstetrics Surgically rep. En-block OHE: – After 5 puppies were rescued with manually, 10 more puppies were rescued with surgery	Surgically rep. En-block OHE: – One puppy was rescued with surgery.	Surgically rep. Routine OHE
Complication	No	Cardiac arrest at surgery She rescued by CPR	No

BW: body weight, CBC: complete blood count, abd.: abdomen, LUH: left uterine horn, RUH: right uterine horn, UB: uterine body, Ut.: uterus, dis.: discharge, PA: placental areas, Rep: replacement, OHE: ovariohysterectomy, CPR: cardiopulmonary resuscitation.

Case Reports: The history of the cases is given below.

In case 1, labor had started seven hours earlier, and one puppy was born alive. While being brought to the hospital due to excessive contractions and lack of parturition, the prolapse and simultaneous UR has been observed by the owner.

Figure 1. Clinical presentation of case 2 (A) and case 3 (B).

In case 2, labor had started 24 hours before she was brought to the clinic, and ended after the delivery of three live puppies, and the mass was seen with the resumption of abdominal contractions.

In case 3, the dog had delivered four live puppies about 40 days ago. A mass in a red color appeared immediately after last puppy had been delivered and disappeared shortly after. The mass seemed once again 20 days after the labor, and it had been rejected manually by the owner due to it did not disappear spontaneously; this process was repeated three more times, and on the fourth and final occasion, the owner presented the dog to the hospital within 24 hours (Figure 1).

In all cases, preoperative fluid (Lactated Ringer's, IV, 10 ml/kg/h, Polifleks®; Polifarma) and antibiotic (Ceftriaxone, IV, 25 mg/kg, Novosef®; Sanofi) treatment was started; the prolapsed mass was washed and cleaned with saline solution (İzoVİP, Polifleks®; Polifarma) and compressed with hyperosmotic fluid (%30 Dekstroz, Polifleks®; Polifarma) for about half an hour to reduce edema; and surgery was performed as the primary treatment method. Unlike other cases, in case 1, the puppies that could be saved manually were delivered in the preoperative process. While en-bloc ovariohysterectomy (OHE) was performed in cases 1 and 2 due to the live puppies, a routine OHE was performed in case 3 (Figure 2). Surgery was performed under general anesthesia in all cases. After induction with propofol (6 mg/kg, Propofol®; Fresenius), anesthesia was continued with isoflurane (Isoflurane USP®, Adeka) and 100% after intubation. Intraoperative analgesia was provided with a constant-rate infusion of a combination of 500 ml saline (İzoVİP, Polifleks®; Polifarma), 30 mg ketamine (Ketasol®, Richter pharma), and 150 mg lidocaine (Adokain®, Sanovel) at a rate of 10 ml/kg/hour. Surgeries were performed with a midline incision. After entering the abdominal cavity, while the prolapsed uterus was pushed through to the inside of the vagina by an assistant externally, it was pulled into the abdominal cavity by the operator, intussusception was corrected, the tissue was restored to its anatomical position, and OHE was performed. The abdominal wall was closed as routinely. Antibiotic treatments were continued for seven days, and stitches were removed ten days after the surgery. A neonatal team immediately intervened and cared about the puppies. The puppies were kept under supervision in an incubator because the Apgar score of all the puppies were <8.

Discussion

In this report, three cases of UPR are discussed; two of which occurred during labor -one of them complicated with uterine rupture- and one of which occurred constantly recurring within 40 days of postpartum.

In canines, uterine horns reside entirely within the abdominal cavity. The uterine body is in both the abdominal and pelvic cavities, and they tethered the dorsolateral body wall and the lateral wall of the pelvic cavity by suspensory ligaments, respectively (Nelissen, 2015). Despite the distinct anatomical positioning of the uterus in dogs compared to humans, UPR in dogs can be similar to pelvic organ prolapse (POP) in humans. Therefore, etiologically, parallels may be drawn with other POPs, such as vaginal prolapse, rectal prolapse, or perineal hernia.

In dogs, the pelvic region bears approximately 36-37% of the body weight and is characterized by a robust framework comprising bone, muscle, and ligaments. In females, the anatomical architecture and functions of the

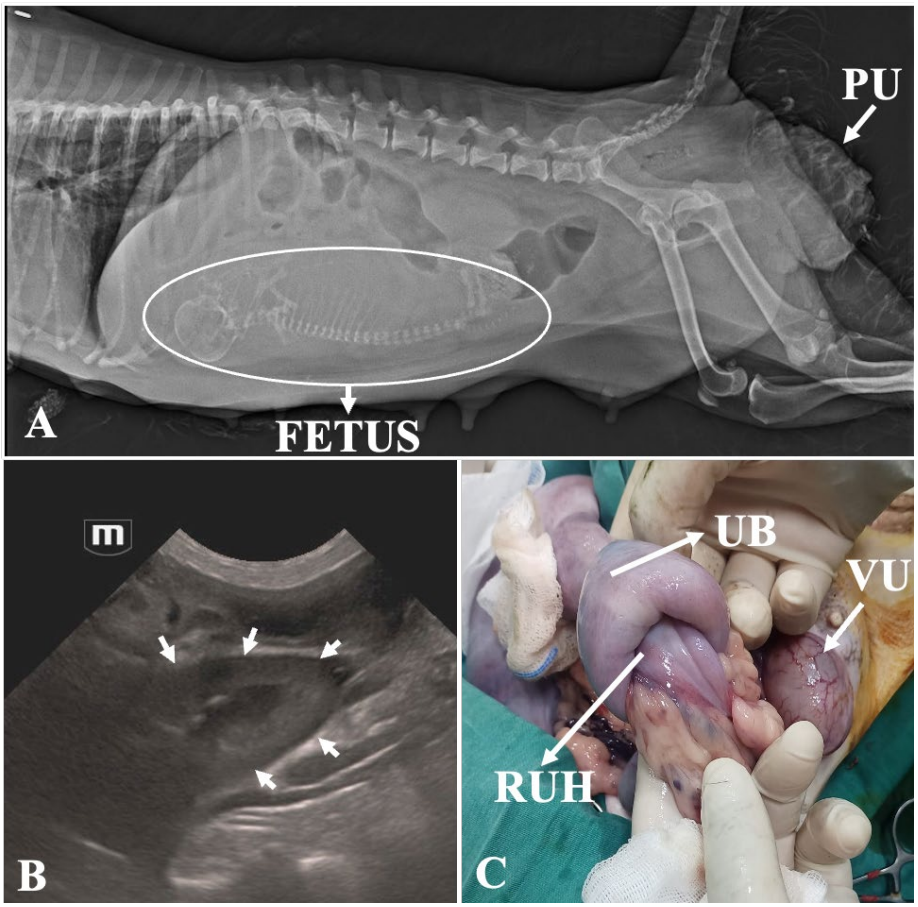

Figure 2. Images belong to case 2. A) The x-ray image of fetus in non-prolapsed uterine horns and uterine prolapse (UPR), B) Ultrasonographic appearance of uterine invagination (white arrows), C) Appearance of invaginated right uterine horn (RUH), uterine body (UB) and vesica urinary (VU) during operation.

pelvis, uterus, and vagina are designed to ensure the uninterrupted continuity of reproduction under optimal conditions. In this design, under the gonadal and non-gonadal effects of hormones such as estrogen (E2), progesterone (P4), and relaxin (RLN), all the reproductive organs must undergo significant anatomical, physiological and histological changes and adapt to pregnancy, labor, and peripartum period. These alterations encompass elongation of the suspensory ligaments to facilitate cranioventral expansion of the uterus concomitant with fetal growth, the capacity of the birth canal to withstand strong abdominal contractions during parturition, cervical dilation to accommodate the regress of fetuses propelled outward by contractions through the birth canal, edema formation in the vulva/vagina, and the physiological separation of the symphysis pelvis. These adaptive responses are examples of the requisite synchrony for successful reproduction.

Although the etiology of POP, such as UPR in humans and animals, remains unclear, there are common points, such as excessive relaxation/stretching of pelvic ligaments, dystocia, excessive abdominal contractions/straining. These factors can be considered macro-predisposing factors, but more recent studies have focused on the organization and abnormal structure of the connective tissue of the pelvic structure and uterosacral ligaments (Zhang et al., 2020). The macro-predisposing factors are shaped by tension, compression, and shear stresses that cause anatomical/physiological changes. They are referred to as mechanical forces at the cellular and subcellular levels. The complex structure and organization of the extracellular matrix (ECM) provides resistance to the mechanical load resulting from daily physiological activity, offers physical support to the cells, and determines the physical properties and behavior of the tissue. The ECM, whose main elements are proteoglycans and collagen, elastin, fibrous proteins, fibronectin, and laminin, organize to form rope-like that confers enormous tensile strength to tendons. Architecture also has the ability to degenerate and reorganize in response to physiological and pathophysiological processes in the same tissue (Karsdal et al., 2013). This dynamic structure is critical in processes such as pregnancy, labor, cervical ripening, and involution in the reproductive system. The most important component of ECM supporting the stability and plasticity of the pelvic floor is collagen synthesized by fibroblasts, with type I providing the mechanical tension, and type III providing the flexibility (Nallasamy et al., 2017). In these processes, weakening the supporting structures strength due to the alteration of the ECM architecture contributes to POP (Zhang et al., 2020), and in addition of gonadal activities, sex hormones also play a role with non-

gonadal or metabolic activities in organizing the macro-changes specific to pregnancy and parturition (Nallasamy et al., 2017). Here, E2 effects on muscle and connective tissue (Fede et al., 2019), and P4 may induces diabetes mellitus which is altering connective tissue function and structure by affecting collagen type I (Módena et al., 2016). Exposure of dogs to P4 during prolonged diestrus, even if not pregnant, may be effective in this regard (Johnston et al., 2001). Relaxin could induce relaxation of the pelvic ligaments and remodeling of the symphysis pelvis, which is associated with collagen degradation (Binli et al., 2023). The mechanism of ECM degradation is not clearly understood. However, this process depends on the combined activity of matrix metalloproteases (MMPs) and their regulation of the release, activation, or retention of growth factors, growth factor binding proteins, cell surface receptors, and cell-cell adhesion molecules. All collagens, especially collagen types I and III, can be degraded by MMPs such as MMP-2 and MMP-9 (Guler and Roovers, 2022). The balance between collagen synthesis and degradation is important for maintaining tissue integrity and tensile strength during continuous tissue remodeling, and disruption of this balance can lead to POP; for example, an increased type I/type III ratio has been found in prolapsed organs of women with POP (Sansilvestri-Morel et al., 2001). In addition, fibroblasts in prolapsed tissue have been found to produce more collagen, MMP-2 and MMP-9 activity increases, tissue inhibitors of metalloproteinases-1 (TIMP-1) activity decreases, and collagen turnover increases (Guler and Roovers, 2022). As this is a case report, we will not go into further molecular detail but will briefly mention the effects of sex hormones on MMP and collagen activity. Studies show that E2 increases connective tissue turnover in the pelvic floor, upregulates MMPs not all and causes an increase in ECM destruction by suppressing TIMPs, suppresses fibroblast proliferation, and increases MMP-2 activity (Fede et al., 2019; Kanca et al., 2011). Progesterone increases MMP-2 activity and decreases MMP-9 activity (Kanca et al., 2011) and, when combined with E2, causes a decrease in the active form of MMP-1 (Zong et al., 2007). Due to its collagenolytic effect, RLN alters ligament mechanics by releasing the MMP activators collagenase, causing induction of collagen type 1 in the symphysis pelvis, inducing MMP1 and MMP-3 expression while showing little effect on TIMPs (Kapila and Xie, 1998).

The role of sex hormones and repeated exposure to them in the etiology of POP is clear. Indeed, the likelihood of UPR in women increases with parity and age (Schulten et al., 2022). The fact that two of our cases (cases 1 and 2) were four years old and multiparous suggests that age and parity may be necessary in the etiology of UPR in dogs, causing repeated exposure to sex hormones and the pregnancy process. On the other hand, the fact that both our case 3 and the case in a previous report (Ağaoğlu et al., 2012) were young (2 years old) and primiparous rules out the importance of repeated exposure to sex hormones alone and even suggests that other factors. In fact, rectal prolapse in dogs often occurs in young animals (< 11 months of age) and is reported to be more common in males, in cases of severe tenesmus, and in only 6% of cases because of dystocia (Igna et al., 2021). These data, as stated in the previous literature (Binli et al., 2021), show that the effect of mechanical forces caused by excessive pushing during parturition increased abdominal tension due to tenesmus, inappropriate oxytocin treatment, or inappropriate obstetric maneuvers affecting the pelvic structures is also essential. In the reports we encountered, there were no attempts to assist parturition, such as oxytocin treatment or obstetric maneuvers. Therefore, we believe that hormonal factors and parturition play a role in the etiology of the cases presented here, not alone but combined with other factors: Body condition score (BCS) and genetic predisposition.

In case 1, the Kangal weighed 28 kg; in case 3, the French Bulldog weighed 6.5 kg. However, adult body weights should be 50-60 kg for the Kangal and 9-13 kg for the French Bulldog. On the other hand, Pekinese (case 2) weighed 7 kg, slightly above the required range of 3.2-6.4 kg. Overweight in women are known to have significant effects on uterine and vaginal prolapse (Myers et al., 2012). Weight loss and weight gain lead to lean mass changes, including adipose tissue and muscle. The ECM is directly linked to weight gain/loss, and adipose tissue plays a vital role in this process. The adipocyte can be expressed as a single fat droplet surrounded by a thick ECM, and the ECM around the adipocyte, which shrinks due to weight loss, is expected to adapt to changes in cell volume. This process can lead to tension and cellular stress. During long-term weight loss, a downregulation in genes that regulate the ECM in adipose tissue and changes in the expression levels of ECM components can be observed (Roumans et al., 2015). Based on this information, we believe that a poor BCS in cases 1 and 3 may have contributed to the formation of the case by negatively affecting the ECM structure.

Assessing age and breed predisposition is difficult because UPR cases are rare in dogs (Payan-Carreira et al., 2012). We agree with this opinion because the small number of cases/reports in dogs does not allow a comprehensive evaluation of UPR, such as a systematic review or meta-analysis. On the other hand, as two of our cases (case 2 and case 3) were small breeds and brachycephalic, we speculate that there may be a breed predisposition in the case. Although UPR has been reported in different breeds such as Pomeranian Spitz (Mashhadi et al., 2024), American Bully (Angrimani et al., 2020) and Great Dane (Sathiamoorhyt et al., 2013), we speculate that vaginal prolapse (Nelissen, 2015) and inguinal hernia (Binli et al., 2023) in dogs may be predisposed by age, small size and brachycephalic breed. This speculation was also supported by a report on mares and cows: Arabian mares (Boye et al., 2022) and beef cows (Peter, 2014) are more prone to UPR than other mares and dairy cows. On the other hand, it is clear that this speculation needs to be supported by genetic studies, and genetic studies in human medicine support our speculation. It has been found that women with a family history of POP are more likely to develop POP than those without. Twin studies have shown that genetic factors account for about 43% of the variation in susceptibility to POPs. Several genetic variants or polymorphisms that play a role in prolapse by affecting collagen synthesis and ECM remodeling have been

identified in women (Lim et al., 2014). We believe that this topic warrants further investigation in veterinary medicine.

Uterine rupture is an emergent and uncommon situation. Some of the predisposing factors that claim to UPR cases also available to uterine rupture. Although factors such as uterine torsion and trauma are the most important, conditions such as prolonged dystocia and pyometra, which make the uterine wall thin and fragile, also play an important role in etiology (Johnston et al., 2001). Although superfecundation and multiple pregnancies are common in dogs, a pregnancy with 16 puppies, as seen in case 1, can be considered unusual and may have resulted in rupture due to excessive stretching on the uterine wall. At the same time, the incidence of dystocia in dogs can be up to 100% in predisposed breeds. Uterine inertia is the most common cause of dystocia. While complete primary uterine inertia does not begin, incomplete primary uterine inertia begins and ends after a few fetuses have been delivered (Gendler et al., 2007). Factors involved include vaginal hyperplasia, vaginal or uterine prolapse, which usually results in a narrowing or obstruction of the birth canal (Gendler et al., 2007), and UPR is responsible for 0.6% of maternal dystocia (Feldman and Nelson, 2004). Case 1 was considered as an incomplete primary uterine inertia case because labor started, and a puppy was born. In this case, the uterus ruptured and prolapsed after continued excessive stretching, and the factors mentioned above, such as ECM architecture and BCS, also contributed. Unlike the Kangal, our other two cases belong to breeds predisposed to dystocia (Johnston et al., 2001). In case 2, the interruption of labor and the onset of labor after 24 hours of rest suggest incomplete primary uterine inertia in this case. It is known that pelvic disharmony and uterine inertia are common in breeds predisposed to dystocia (Johnston et al., 2001), and it is also known that uterine relaxation and uterine inertia provided by P4 may lead to UPR in women (Módena et al., 2016) and cows (Peter, 2014).

Treatment might be performed medically or surgically, and when deciding on the treatment method, factors such as the uterus condition, the animal's breeding value, and the owner's wishes are considered. We believe that even if the uterus is successfully replaced by medical treatment, there is a possibility of recurrence due to excessive stretching of the suspensory and pelvic ligaments, and this risk is even higher in a future pregnancy. It should also be considered that if pregnancy is not achieved, uterine pathologies such as pyometra may develop, as the prolapsed uterus is open to trauma, environmental conditions, and bacterial contamination. Uterine prolapse complicated with CEH suggests that the possibility of recurrence may be increased if pyometra develops. In a Great Dane with bilateral UPR, manual placement was reported to be successful with no short-term complications, but no information was provided on the long-term follow-up (Sathiamoorthy et al., 2013). In contrast to this case, the recurrence of the case after manual treatment in a Pomeranian Spitz (Mashhadi et al., 2024), and in case 3 presented here, leads us to question the validity of manual rejection in the treatment in dogs. The reason for the success of manual repositioning of UPR in cows is that the birth canal is sufficiently large and wide to allow manual treatment. In this case, Sathiamoorthy et al. (2013) attributed the procedure's success to the animal's pelvic floor size, which allowed for manual intervention. Both our case and Mashhadi et al. (2024) suggest that manual therapy is unsuccessful in small breeds.

On the other hand, there is the possibility of vascular congestion due to intussusception and consequent devitalization or ischemia-reperfusion injury (Zitkute et al., 2021). Intussusception is challenging to regulate as hemodynamics cannot be easily altered, and invasive procedures are required. Considering the above reasons, we agree with the publications reporting that the most appropriate treatment intervention in UPR is surgery (Greiling et al., 2023; Payan-Carreira et al., 2012), especially OHE which also prevents the transmission of a possible genetic predisposition.

Because UPR can lead to life-threatening conditions, precautions, and practices should be implemented for emergency intervention during the perioperative period. In case 2, although none of the above risks were present and the necessary perioperative precautions were taken, cardiac arrest occurred during the surgery. However, she was revived, there were no post-operative complications, and subsequent follow-up via telephone survey showed that she remained in good health. Considering that brachycephalic breeds such as Pekingese have a 1.57-fold increase in intra-anesthetic complication rate and a 4.33-fold increase in post-anesthetic complication rate than non-brachycephalic breeds (Gruenheid et al., 2018), we believe that the complication experienced was due to brachycephalic airway syndrome.

As a result, UPR in dogs is an obstetric condition that needs alertness because it is life-threatening, it is rarely seen, and it is impossible to take precautions (except elective OHE). On the other hand, mother and/or puppies can be survived with timely and appropriate surgical management. The etiology of UPR is not fully understood, but it is undoubtedly multifactorial in dogs. It seems that sex hormones, which cause significant changes in the ECM architecture of the pelvic floor and ligaments, are the main factors. However, we believe, and speculated here, that there are co-factors, including poor BCS, age, parity, and breed predisposition, that also contribute significantly to UPR etiology. However, to clearly define both the primary factors and co-factors speculated by this report, further research is required to investigate the effect of hormones, age, parity, and breed on ECM architecture of the pelvic floor and reproductive tract.

Conflict of Interest

The authors stated that they did not have anyreal, potential or perceived conflict of interest.

Ethical Approval

This work involved the use of non-experimental animal only. Established internationally recognized high standards

of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not necessarily required.

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