Review Article

Canine Urinary Incontinence Post-neutering: A Review of Associated Factors, Pathophysiology and Treatment Options

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Abstract

Canine urinary incontinence is commonly encountered in small animal veterinary practice with high prevalence in spayed female dogs. The diagnosis of neutering-induced urinary incontinence is usually based on clinical signs, history and elimination of other possible diagnoses. The proposed predispositions to incontinence that follows neutering including gender, breed, body weight, obesity, tail docking, spaying technique (ovariectomy and ovariohysterectomy) and morphology of the LUT, e.g. the position of neck of the bladder and urethral length, have all been investigated. At present, the exact underlying mechanisms are not fully understood. However, it is widely agreed that the condition is multi-factorial and hormone-associated. The role of gonadotrophin LH and FSH in the physiology and/or pathology of the canine lower urinary tract function and its relationship to the development of urinary incontinence post-spay has recently been suggested and remains an interesting subject for further research. Medical approach is the mainstay of treatment for affected animals with surgical correction being considered when medical treatment fails to restore continence or patient is unsuitable for long-term medication. Medical and surgical options in the treatment of post-neutering urinary incontinence are reviewed.

Keywords: dog, gonadectomy, urinary incontinence

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บทคัดย่อ

ภาวะปัสสาวะเล็ดในสุนัขหลังทำหมัน: ปัจจัยที่เกี่ยวข้อง พยาธิสรีรวิทยา และการรักษา

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ภาวะปัสสาวะเล็ดในสุนัขเป็นปัญหาที่พบได้บ่อยทางคลินิก โดยเฉพาะสุนัขเพศเมียที่ได้รับการทำหมันแล้ว การวินิจฉัยโรคทำได้จากการซักประวัติที่เกี่ยวข้อง อาการที่จำเพาะของโรค และการตัดสาเหตุจากปัญหาอื่นที่ทำให้สุนัขแสดงอาการปัสสาวะบ่อยหรือปัสสาวะเล็ด ปัจจัยโน้มนำของโรคที่มีการศึกษา ได้แก่ สายพันธุ์ น้ำหนัก ความอ้วน การตัดหาง เทคนิคการทำหมันที่แตกต่างกันระหว่างการตัดรังไข่ออกเพียงอย่างเดียวหรือการตัดทั้งรังไข่และมดลูก ตลอดจนลักษณะทางกายวิภาคของกระเพาะปัสสาวะและท่อปัสสาวะส่วนต้นที่เปลี่ยนแปลงภายหลังการทำหมัน ในปัจจุบันแม้จะยังไม่ทราบอย่างแน่ชัดถึงสาเหตุของการเกิดภาวะปัสสาวะเล็ดในสุนัขหลังทำหมัน แต่เป็นที่ยอมรับว่าอาการดังกล่าวเกิดจากหลายปัจจัยร่วมกัน รวมถึงปัจจัยด้านการเปลี่ยนแปลงของฮอร์โมนหลังทำหมัน บทบาทของโกนาโดโทรปิน ได้แก่ ลูทีไนซิง ฮอร์โมน และฟอลลิเคิล สะติมูเลติง ฮอร์โมน ต่อการทำงานของระบบขับถ่ายปัสสาวะส่วนล่างและความสัมพันธ์กับการเกิดภาวะปัสสาวะเล็ดเป็นอีกอีกหนึ่งปัจจัยที่ได้รับความสนใจและควรศึกษาต่อไปในอนาคต การรักษาสามารถทำได้ทั้งการรักษาทางยาและการผ่าตัด โดยจะพิจารณาผ่าตัดแก้ไขหากการรักษาทางยาไม่ได้ผลดีหรือสุนัขมีปัญหาสุขภาพที่ไม่เหมาะสมกับการได้รับยาเป็นระยะเวลานาน ซึ่งทางเลือกของการรักษาได้กล่าวในบทความ

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Introduction

Urinary incontinence usually refers to the lack of voluntary control over the flow of urine during the storage phase of urination. As a result, there is leakage of urine when there is no intention to urinate. In humans, according to the International Continence Society (1988), urinary incontinence is defined as objectively demonstrable involuntary loss of urine that is a social or hygienic problem.

In dogs, urinary incontinence is commonly encountered in small animal veterinary practice. It is considered a welfare problem and can be a lifelong condition that requires medication on a daily basis. If the problem cannot be solved, it results in suffering of the incontinent animal, and an untenable situation for pet owners. Because animals with such a condition may dribble urine intermittently or even constantly, their hindquarters are wet, soaked with urine or saliva from licking themselves clean. Skin disorders such as rashes, severe infectious dermatitis or ulcers around the perineal area, together with an unpleasant odor, often are major and unpleasant consequences. Animals with urinary incontinence usually require extensive daily nursing care and great patience on the part of their owners. In some cases, euthanasia of the pet may eventually be requested if the problem cannot be managed successfully.

Aetiology of canine urinary incontinence

The function of the lower urinary tract (LUT) is regulated by the central and peripheral autonomic and somatic nervous systems. However, other modifying factors such as the integrity of the bladder and urethral wall as well as reproductive hormones also have important roles in the function of the LUT.
Urinary incontinence may result from a variety of conditions. Abnormal increases in the frequency of urination are sometimes difficult to distinguish from true incontinence. The differential diagnosis of incontinent dogs has been extensively discussed (Holt, 1990[a]; Moreau, 1990; Silverman and Long, 2000). Basically, canine urinary incontinence can be caused by congenital or acquired abnormalities and is categorized as neurogenic or non-neurogenic (Moreau, 1990).

1. *Neurogenic urinary incontinence*

The pathophysiology of neurogenic incontinence varies with the location and severity of

nerve damage (Moreau, 1990). The possible causes of neurogenic incontinence include trauma to the cauda equina or luxations of coccygeal vertebrae resulting from tail injury, spinal fractures, lumbo-sacral spinal canal stenosis, lumbo-sacral malformation and misalignment or diskospondylitis (Silverman and Long, 2000). Upper motor neuron bladder dysfunction, termed as spastic neuropathic bladder, usually results in incomplete emptying of bladder at the time of urination, while with lower motor neuron dysfunction, termed as flaccid neuropathic bladder, the animal has an excessively dilated bladder. Abnormalities of micturition caused by the nervous system, neurogenic urinary incontinence, may be reversible or irreversible. Reversible lesions include spinal cord or peripheral nerve compression. Treatment in these cases is directed toward correction of the primary cause. Irreversible lesions include congenital defects and injuries or diseases associated with neuronal destruction, and treatment depends upon the severity of the underlying problem which is often difficult and discouraging (Moreau, 1990).

2. *Non-neurogenic urinary incontinence*

Various conditions are encountered in non-neurogenic incontinence, i.e. (i) systemic diseases such as diabetes that result in polyuria and polydipsia, (ii) disorders of the urinary bladder that increase the micturition reflex and (iii) administration of diuretics or related drugs including corticosteroids, anticholinergics and antipsychotics (Tsakiris et al., 2008). In this condition, voiding is basically normal, but the storage phase is shortened because the bladder fills more rapidly than normal. The urge to urinate may develop so rapidly and intensely that animals could no longer control urination.

In young dogs, urinary incontinence includes ectopic ureters which are the commonest diagnosis in juvenile female dogs, bladder hypoplasia, intersexuality, patent urachus and congenital incompetence of the urethral sphincter mechanism. An observation shows that about half of the young female dogs with congenital incompetence of urethral sphincter mechanism become continent after their first oestrus (Holt, 1990[b]). In adult dogs, bladder neoplasia, detrusor instability of the bladder, partial urethral obstruction, prostatic disorders and acquired urethral sphincter mechanism incompetence (USMI), weakness of the urinary sphincter, are the main differential diagnoses for incontinent male and female dogs. The latter is the commonest cause of incontinence in adult dogs and is particularly prevalent in spayed bitches (Holt, 1990[a]).

Post-neutering urinary incontinence

Factors associated with the development of post-neutering incontinence

The diagnosis of spay-related incontinence is usually based on typical clinical signs, history and elimination of other possible diagnoses (Holt, 2005). The relationship between neutering and incontinence caused by USMI is widely accepted (Holt, 1990[b]; Arnold, 1993; Holt and Thrusfield, 1993; Power et al., 1998; Thrusfield et al., 1998; Stöcklin-Gautschi et al., 2001; Spain et al., 2004). The time interval between spaying and the onset of incontinence markedly varies from immediate to 9.5 years with an average onset of 2.9 years (Stöcklin-Gautschi et al., 2001). The relative risk in spayed bitches has been documented as high as 7.8 times compared to intact bitches (Thrusfield et al., 1998). This condition affects up to 20% of spayed bitches (Okkens et al., 1997; Thrusfield et al., 1998; Stöcklin-Gautschi et al., 2001; Angioletti et al., 2004), but less than 1% of intact bitches (Holt and Thrusfield, 1993) and is only sporadically reported in male dogs regardless of the gonadal status (intact or gonadectomised). These reports indicate different levels of risk between gonadal statuses and between genders.

The incontinence greatly affects female rather than male population of dogs. It has been reported that 71% of adult and 34% of juvenile dogs referred to investigation of incontinence were diagnosed as USMI, and the majority of adult USMI patients (96.3%) is females (Holt, 1990[b]). Gender differences in the level of risk of the incontinence may be associated with anatomical differences between male and female urethra; the female urethra is shorter, the striated urethral sphincter is smaller and the contractile responses are poorer than those of the male. In addition, the prostate and colliculus seminalis are suggested to contribute to urethral resistance.

The proposed predispositions to post-neutering urinary incontinence in dog including breed, body weight, obesity, gender, spaying technique (ovariectomy and ovariohysterectomy) and morphology of the LUT, e.g. the position of the neck of the bladder and urethral length, have all been investigated (Holt and Thrusfield, 1993; Gregory et al., 1994; Okkens et al., 1997; Angioletti et al., 2004). The affected animals belong predominantly to large and giant breeds. The Bouvier des Flandres, Boxer, Dobermann Pinscher, Irish setter, Old English sheepdog, Rottweiler and Weimaraner are more prone to the development of urinary incontinence (Holt and Thrusfield, 1993).

Overweight dogs are at higher risk. A study showed that bitches that were overweight before spaying had 3.5 times higher risk compared to bitches that were not obese (Angioletti et al., 2004). Incontinence affects 12.5% of bitches with a body weight exceeding 20 kg and 5.1 % of bitches with a body weight of less than 20 kg (Stöcklin-Gautschi et al., 2001).

The delivery of a newborn baby results in pelvic floor muscle injuries during labor and is related to urinary incontinence in human beings. In dogs, there seems to be no connection between the risk of urinary incontinence and parturitions or the number of pregnancies (Janssens and Peeters, 1997). In this regard, tail docking has been suggested as a risk factor because it is believed that docking causes the levator ani and coccygeus muscle atrophy or damage; both muscles are equivalent to pelvic floor muscles. Urinary incontinence is frequently seen in docked dogs such as Boxers, Rottweiller and Dobermans although other breeds with intact tails are also

frequently seen with USMI. However, at present, a study concerning breed-matched groups of docked and undocked dogs to determine the association between docking and the development of incontinence has not yet been reported (Gregory, 1994).

Differences in the techniques used for spaying (ovariectomy or ovariohysterectomy) had been questioned as a causative factor for the development of incontinence. Many retrospective studies have consistently reported no difference in the occurrence of incontinence between the two surgical techniques of spaying (Okkens et al., 1997; Stöcklin-Gautschi et al., 2001; Angioletti et al., 2004). Removal of the cervix is also not shown to be a risk factor for spayed bitches (Thrusfield et al., 1998). Anatomical investigations using radiographs reveal that, regardless of gender, the bladder neck of incontinent dogs is usually intra-pelvic and probably related to the length of the urethra that is significantly shorter in incontinent bitches (Gregory et al., 1992; Power et al., 1998).

The timing of spaying relative to puberty (i.e. pre- or post-first oestrus) is thought to influence the occurrence of incontinence. Despite conflicting results (Thrusfield et al., 1998; Stöcklin-Gautschi et al., 2001; Arnold and Reichler, 2005), an epidemiological study involving a sample size of 1,842 dogs revealed that age at early spaying was associated with different levels of risk in developing urinary incontinence; females spayed after age of 3 months were at lower risk than those spayed before 3 months old (Spain et al., 2004). This may be explained by increased stiffness of the bladder wall that associates with altered composition of extracellular matrix if gonadectomy is performed pre-pubertally (Cabral et al., 2003). Nevertheless, a systematic review concerning the effect of age at neutering on the development of urinary incontinence has recently suggested there is some weak evidence to conclude that neutering, particularly before the age of 3 months, increases the risk of urinary incontinence (Beauvais et al., 2012). For the sake of efficient control of dog population on a large scale, pre-pubertal gonadectomy in dogs is recommended to perform at 3-6 months old.

Pathophysiology of the development of post-neutering incontinence

Previously, several hypotheses were proposed to explain this pathology: (i) the development of adhesions between the neck of bladder and vaginal/uterine stump following ovariohysterectomy, (ii) damage to the supporting structures of the bladder at the time of surgery and (iii) oestrogen deprivation following removal of the ovaries (Gregory, 1994). The exact mechanism for the development of incontinence following removal of the gonads remains unknown, but it is generally accepted that the common cause is the impaired function of urethral closure. The possible association between neutering and incontinence has been proposed to result from a combination of the neurological, vascular and hormonal changes that follow ovariohysterectomy (Gregory, 1994).

Oestrogen insufficiency is accepted to account for the incontinence in both post-menopausal women and spayed bitches. However, the incontinence is not simply due to only oestrogen deficiency because oestrogen deficiency alone seems unlikely to explain all pathophysiological aspects of this symptom. It is evident that a vast majority of bitches that undergo spaying remains continent and therapy with oestrogen supplementation appears to be ineffective in about 35% of affected animals (Janszen et al., 1997; Mandigers and Nell, 2001). Long-term contraceptive treatments with progestins that chronically lower plasma oestrogen concentrations and induces ovarian atrophy have never been reported to cause incontinence in progestin-treated bitches (De Bosschere at al., 2002). Furthermore, the response to oestrogen replacement therapy often eventually ceases, in spite of increasing the dosage (Holt, 1990[a]). In humans, although a significant subjective improvement in incontinence after oestrogen therapy is reported, some controlled studies using urodynamic assessments show no objective improvement (Blakeman et al., 2000). In addition, the concentrations of plasma oestrogen in spayed bitches with incontinence (2.8-5.3 pg/ml) and intact healthy anoestrous bitches (3.2-6.5 pg/ml) are not significantly different (Nickel, 1998).

Based on the fact that gonadectomy affects hormonal homeostasis which contributes to a reduction in sex steroid hormones and an increase in the gonadotrophins (i.e., LH and FSH) in both male and female dogs (Olson et al., 1992; Colon et al., 1993; Concannon, 1993; Reichler et al., 2004), a considerable increase in circulating LH and FSH following gonadectomy raises the question whether these changes are responsible for the development of urinary incontinence as this condition mainly affects spayed bitches rather than intact bitches (Reichler et al., 2003).

Intriguingly, lowering plasma LH and FSH concentrations by GnRH agonists/antagonists treatment in post-spay incontinent bitches that have not responded to classic medical treatments (i.e. oestrogen therapy or alpha-adrenergic receptor agonists) have shown in 12 out of 13 bitches a temporary return to continence or an improvement of symptoms irrespective of the duration of prior incontinence (Reichler et al., 2003). These findings put forward a new insight into the development of this condition implying that gonadotrophin LH and FSH have a role in the LUT function and changes in hormone patterns post-neutering affect the pathophysiology of LUT leading to the development of incontinence. Recently, a series of studies on a possible role of gonadotrophin LH and FSH in the lower urinary tract of dogs has been carried out. Receptors for LH and FSH are present in the urinary bladder and urethra of normal healthy male and female dogs (Ponglowhapan et al., 2007). Differences between intact and gonadectomised dogs in the expression of LH and FSH receptor (Ponglowhapan et al., 2008[a]; Reichler and Welle, 2005), COX-2 (Ponglowhapan et al., 2009[a]), prostaglandin E_2 receptor subtypes (Ponglowhapan et al., 2010) and in the proportion of collagen and muscle

(Ponglowhapan et al., 2008[b]) as well as glycosaminoglycan profile (Ponglowhapan et al., 2011) in the urinary bladder and urethra substantiate possible roles of gonadotrophins in the development of this condition (Ponglowhapan, 2009[b]).

Apart from hormone-induced structural changes in the LUT of neutered dogs, functions of the LUT, i.e. maximal urethral closure pressure (MUCP) and functional urethral length, are compromised after neutering (Nickel, 1998; Reichler et al., 2004; Salomon et al., 2006). It is interesting to note that although structural and functional changes in the LUT are consistently observed, a large majority of spayed bitches remain continent. This may indicate that the LUT function is compromised only to an extent that still allows the majority of spayed dog population to achieve continence.

Treatment options for neutering-induced urinary incontinence

The incontinence may be considered a minor problem by some owners particularly if the dog is left outside the house. Nevertheless, the consequences of the clinical sign, nursing care, option for treatment and side effects of any medication have to be clearly discussed between veterinarian and pet owner because it is a lifelong problem and treatment option must be adjusted for each individual dog.

1. Medical treatment

Basically, medical management is the first line of treatment because of its non-invasive approach with surgical intervention being considered for non-responsive or those unsuitable for long-term pharmaceutical administration. The use of phenylpropanolamine (PPA), the alpha-adrenergic agonist, or oestrogen replacement therapy or the combinations of them have long been recommended in most cases. They increase urethral resistance and tone through smooth muscle contraction, resulting in a resolution or reduction in the episode of incontinence (Hamaide et al., 2006). In addition, alpha-adrenergic agonists act on alpha-adrenergic receptors of the bladder neck and proximal urethra and oestrogen enhances the sensitivity of alpha-adrenergic receptors to alpha agonists.

Studies have shown that the success rate for the reversal of incontinence in spayed bitches was between 85-92% following treatment with PPA (Scott et al., 2002; Reichler et al., 2006) compared with 65-82% for oestrogen replacement therapy using oestriol (Janszen et al., 1997; Mandigers and Nell, 2001). A combination of PPA and oestrogen are basically thought to provide a synergistic effect on increasing urethral tone, but significant clinical improvement was found in some incontinent bitches and urodynamic evaluation revealed no differences in MUCP values between bitches treated with the combinations and those treated with oestrogen alone (Hamaide et al., 2006).

Oestrogenic effects such as swelling of the vulva and attractiveness to male dogs have been reported soon after the treatment with higher dose oestriol (Mandigers and Nell, 2001). Advised dosage of oestriol is adjustable depending on clinical response of each animal. Recently, a single daily dose of 1.5 mg/kg bodyweight of PPA is shown to be effective to treat incontinent bitches (Claeys et al., 2011). Despite its high efficacy in treatment of canine urinary incontinence post-neutering, PPA is nowadays no longer sold without a prescription due to a proposed increased risk of haemorrhagic stroke in humans or has been withdrawn from the market in many countries. Pseudoephedrine (PD), an alpha-agonist and stereoisomer of ephedrine, has become a treatment of choices because it is cost-effective and available in the market. Some incontinent dogs clinically improved after PD administration; however, lack of significant changes in urodynamic variables and owner perception of continence as well as the increased incidence of adverse effects including panting, decreased appetite and lethargy make PD a less satisfactory alternative to PPA for the treatment in incontinent female dogs (Byron et al., 2007).

Drugs used for incontinent dogs should be administrated with caution because of their long-term use and adverse side effects that include cardiovascular effects such as hypertension, cardiac arrhythmias for alpha-adrenergic agonists (PPA and PD), and bone marrow suppression for chronic use of oestriol. In particular the use of oestrogen replacement therapy in ovariectomised bitches having urinary incontinence is prohibited due to high risk in cystic endometrial hyperplasia and pyometra complex.

The lack of a highly effective conventional medical treatment stimulates research interest into the underlying pathophysiology of the development of spay-induced incontinence in the dog and into the development of new and more effective treatments. When GnRH agonists were used to treat spayed incontinent bitches, the continence was restored or improvement of the symptom was observed during the period that plasma LH and FSH concentrations had been suppressed (Reichler et al., 2003; Reichler et al., 2006). The use of slow-release GnRH agonist, e.g deslorelin implantation, is a practical alternative of medical approaches to spay-related incontinence in the dog. It has been proposed that GnRH agonist may help improve physiological function of the bladder rather than the urethral (Reichler et al., 2006) through GnRH, LH and/or FSH receptors (Reichler and Welle, 2005; Ponglowhapan, 2009[b]).

2. Surgical treatment

As USMI is mainly responsible for the development of urinary incontinence in spayed bitches, the goal of surgical treatment is to correct weakness of the urethral wall, thus increasing urethral sphincter resistance to the outflow of urine by (i) providing improved MUCP to create urethral resistance (colposuspension, urethropexy, urethral lengthening, intra-urethral injection of bulking agents) and/or (ii) improving functional urethral length (colposuspension, urethral lengthening) (Holt, 2005; McLoughlin and Chew, 2009).

Among the surgical techniques, colposuspension is most commonly performed, either alone or combined with medical treatment. Combined medical-surgical approaches to treatment of USMI have shown a pronounced improvement or a complete cure of the symptom (Rawlings et al., 2001). The objective of colposuspension is to relocate the intra-pelvic bladder neck to an intra-abdominal position by placing of non-absorbable sutures between the vagina and the prepubic tendon (Holt, 1990[c]). Immediately after surgery, urethral pressure profiles improves, i.e. MUCP decreases, functional profile length increases (Rawlings et al., 2000). Long-term observation of 22 incontinent bitches showed that the continence was completely restored in 15 bitches and an overview of client satisfaction was as high as 86% (19/22) (Rawlings et al., 2001). Other surgical procedures have been documented, but according to a low number of cases the results are in variable success rates.

Conclusion

Urinary incontinence is a serious and lifelong condition that is more prevalent in spayed bitches. To date, the underlying pathophysiological mechanisms are not fully understood. Nonetheless, it is agreed that the condition is multi-factorial and hormone-associated. Other predisposing factors, e.g. breed and obesity, must also be taken into account. Although for many years medical treatments such as the use PPA or oestrogen replacement therapy have been the mainstay of treatment for the majority of incontinent spayed bitches, some responded poorly to these treatments. New insights into the role of gonadotrophins in the LUT function and the practical and successful use of a sustained-release formulation of a potent GnRH agonist in incontinent spayed bitches have been reported in a number of recent studies. Surgical correction of USMI is considered when medical approach fails to restore continence or the patient is unsuitable for long-term medication.

References

Angioletti, A., De Francesco, I., Vergottini, M. and Battocchio, M.L. 2004. Urinary incontinence after spaying in the bitch: incidence and oestrogen-therapy. Vet Res Commun. 1: 153-155.

Arnold, S. 1993. Relation of incontinence to neutering. J Reprod Fertil Suppl.47: 547.

Arnold, S. and Reichler, I.M. 2005. USMI: Pathophysiology, diagnosis and non-surgical treatment. In: Proceedings of 48th Annual Congress of The British Small Animal Veterinary Association. Birmingham, UK. 225-228.

Beauvais, W., Cardwell, J.M. and Brodbelt, D.C. 2012. The effect of neutering on the risk of urinary incontinence in bitches – a systematic review. J Small Anim Pract. 53: 198-204.

Blakeman, P.J., Hilton, P. and Bulmer, J.N. 2000. Oestrogen and progesterone receptor expression in the female lower urinary tract, with reference to oestrogen status. BJU Int. 86: 32-38.

Byron, J.K., March, P.A., Chew, D.J. and DiBartola, S.P. 2007. Effect of phenylpropanolamine and pseudoephedrine on the urethral pressure profile and continence scores of incontinent female dogs. J Vet Intern Med. 21: 47–53.

Cabral, C.A., Sampaio, F.J. and Cardoso, L.E. 2003. Analysis of the modifications in the composition of bladder glycosaminoglycan and collagen as a consequence of changes in sex hormones associated with puberty or oophorectomy in female rats. J Urol. 170: 2512-2516.

Claeys, S., Rustichelli, F., Noël, S. and Hamaide, A. 2011. Clinical evaluation of a single daily dose of phenylpropanolamine in the treatment of urethral sphincter mechanism incompetence in the bitch. Can Vet J. 52: 501-505.

Colon, J., Kimball, M., Hansen,B. and Concannon, P.W. 1993. Effects of contraceptive doses of the progestagenmegestrol acetate on luteinizing hormone and follicle-stimulating hormone secretion in female dogs. J Reprod Fertil Suppl. 47: 519-521.

Concannon, P.W. 1993. Biology of gonadotrophin secretion in adult and prepubertal female dogs. J Reprod Fertil Suppl. 47: 3-27.

De Bosschere, H., Ducatelle, R., Tshamala, M. and Coryn, M.2002.Changes in sex hormone receptors during administration of progesterone to prevent estrus in the bitch.Theriogenology.58: 1209-1217.

Gregory, S.P., Parkinson, T.J. and Holt, P.E. 1992. Urethral conformation and position in relation to urinary incontinence in the bitch. Vet Rec. 131: 167-170.

Gregory, S.P. 1994. Developments in the understanding of the pathophysiology of urethral sphincter mechanism in competence in the bitch. Br Vet J. 150: 135-150.

Hamaide, A.J., Grand, J.G., Farnir, F., Le Couls, G., Snaps, F.R., Balligand, M.H., Verstegen, J.P. 2006.Urodynamic and morphologic changes in the lower portion of the urogenital tract after administration of estriol alone and in combination with phenylpropanolamine in sexually intact and spayed female dogs. Am J Vet Res. 67: 901-908.

Holt, P.E. 1990[a]. Urinary incontinence in the bitch. Vet Rec. 127: 604.

Holt, P.E. 1990[b]. Urinary incontinence in dogs and cats. Vet Rec. 127: 347-350.

Holt, P.E. 1990[c]. Long-term evaluation of colposuspension in the treatment of urinary incontinence due to incompetence of the urethral sphincter mechanism in the bitch. Vet Rec. 127: 537-542.

Holt, P.E. and Thrusfield, M.V. 1993. Association in bitches between breed, size, neutering and docking, and acquired urinary incontinence due to incompetence of the urethral sphincter mechanism. Vet Rec. 133: 177-180.

Holt, P.E. 2005. USMI: Diagnostic pitfalls and surgical options. In: Proceedings of 48th annual congress of The British small animal veterinary association. Birmingham, UK. 229-230.

Janssens, L.A. and Peeters, S. 1997. Comparisons between stress incontinence in women and

sphincter mechanism incompetence in the female dog. Vet Rec. 141: 620-625.

Janszen, B.P.M., vanLaar, P.H. and Bergman, J.G.H.E. 1997. Treatment of urinary incontinence in the bitch: A pilot field study with Incurin®. Vet Q. 19: S42-S42.

Mandigers, R.J. and Nell, T. 2001. Treatment of bitches with acquired urinary incontinence with oestriol. Vet Rec. 149: 764-767.

McLoughlin, M.A. and Chew, D.J. 2009. Surgical treatment of urethral sphincter mechanism incompetence in female dogs. Comp Cont Edu Vet.: 360-373.

Moreau, P.M. 1990. Disorders of the lower urinary tract in old dogs. Vet Rec. 126: 415-425.

Nickel, R.F. 1998.Studies on the function of the urethra and bladder in continent and incontinent female dogs. In: PhD Thesis. University of Utrecht.

Okkens, A.C., Kooistra, H.S. and Nickel, R.F. 1997.Comparison of long-term effects of ovariectomy versus ovariohysterectomy in bitches. J Reprod Fertil Suppl. 51: 227-231.

Olson, P.N., Mulnix, J.A. and Nett, T.M. 1992.Concentrations of luteinizing hormone and follicle-stimulating hormone in the serum of sexually intact and neutered dogs. Am J Vet Res. 53: 762-766.

Ponglowhapan, S., Church, D.B., Scaramuzzi, R.J. and Khalid, M. 2007. Luteinizing hormone and follicle-stimulating hormone receptors and their transcribed genes (mRNA) are present in the lower urinary tract of intact male and female dogs. Theriogenology.67: 353-366.

Ponglowhapan, S., Church, D.B. and Khalid, M. 2008[a].Differences in the expression of luteinizing hormone and follicle-stimulating hormone receptors in the lower urinary tract between intact and gonadectomised male and female dogs. Domest Anim Endocrinol. 34: 339-351.

Ponglowhapan, S., Church, D.B. and Khalid, M. 2008[b].Differences in the proportion of collagen and muscle in the canine lower urinary tract with regard to gonadal status and gender. Theriogenology. 70: 1516-1524.

Ponglowhapan, S., Church, D.B. and Khalid, M. 2009[a].Expression of cyclooxygenase-2 in the canine lower urinary tract with regard to the effects of gonadal status and gender. Theriogenology. 71: 1276-1288.

Ponglowhapan, S. 2009[b]. The potential role of gonadotrophins in the lower urinary tract of dogs with particular emphasis on differences between intact and gonadectomised animals. In: PhD Thesis. The Royal Veterinary College, University of London.

Ponglowhapan, S., Church, D.B. and Khalid, M. 2010.Expression of prostaglandin E_2 receptor subtypes in the canine lower urinary tract varies according to the gonadal status and gender. Theriogenology. 74: 1450-1466.

Ponglowhapan, S., Church, D.B. and Khalid, M. 2011. Effect of the gonadal status and the gender on glycosaminoglycans profile in the lower urinary tract of dogs. Theriogenology. 76:1284-1292.

Power, S.C., Eggleton, K.E., Aaron, A.J., Holt, P.E. and Cripps, P.J. 1998. Urethral sphincter mechanism incompetence in the male dog: importance of bladder neck position, proximal urethral length and castration. J Small Anim Pract. 39: 69-72.

Rawlings, C.A., Mahaffey, M.B., Chernosky, A. And Huzella, L. 2000. Immediate urodynamic and anatomic response to colposuspension in female Beagles. Am J Vet Res. 61: 1353-1357.

Rawlings, C., Barsanti, J.A., Mahaffey, M.B. and Bement, S. 2001.Evaluation of colposuspension for treatment of incontinence in spayed female dogs. J Am Vet Med Assoc. 219: 770-775.

Reichler, I.M., Hubler, M., Jöchle, W., Trigg, T.E., Piché, C.A. and Arnold, S. 2003. The effect of GnRH analogs on urinary incontinence after ablation of the ovaries in dogs. Theriogenology. 60: 1207-1216.

Reichler, I.M., Pfeiffer, E., Piché, C.A., Jöchle, W., Roos, M., Hubler, M. and Arnold, S. 2004. Changes in plasma gonadotropin concentrations and urethral closure pressure in the bitch during the 12 months following ovariectomy. Theriogenology. 62: 1391-1402.

Reichler, I.M. and Welle, M. 2005. Influence of spaying on the expression of GnRH-, FSH- and LH-receptors of the urinary tract of the bitch. Reprod Domest Anim. 40: 350.

Reichler, I.M., Jöchle, W., Piché, C.A., Roos, M. and Arnold, S. 2006. Effect of a long acting GnRH analogue or placebo on plasma LH/FSH, urethral pressure profiles and clinical signs of urinary incontinence due to sphincter mechanism incompetence in bitches. Theriogenology. 66: 1227-1236.

Salomon, J.F., Gouriou,M., Dutot, E., Borenstein, N. And Combrisson, H. 2006. Experimental study of urodynamic changes after ovariectomy in 10 dogs. Vet Rec.159: 807-811.

Scott, L., Leddy, M., Bernay, F. and Davot, J.L.2002. Evaluation of phenylpropanolamine in the treatment of urethral sphincter mechanism incompetence in the bitch. J Small Anim Pract. 43: 493-496.

Silverman, S. and Long, C.D. 2000. The diagnosis of urinary incontinence and abnormal urination in dogs and cats. Vet Clin North Am Small Anim Pract. 30: 427-448.

Spain, C.V., Scarlett, J.M. and Houpt, K.A. 2004. Long-term risks and benefits of early-age gonadectomy in dogs. J Am Vet Med Assoc. 224: 380-387.

Stöcklin-Gautschi, N.M., Hässig, M., Reichler, I.M., Hubler, M. and Arnold, S. 2001.The relationship of urinary incontinence to early spaying in bitches. J Reprod Fertil Suppl. 57: 233-236.

Thrusfield, M.V., Holt, P.E. and Muirhead, R.H. 1998. Acquired urinary incontinence in bitches: its incidences and relationship to neutering practices. J Small Anim Pract. 39: 559-566.

Tsakiris, P., Oelke, M. and Michel, M.C. 2008.Drug-induced urinary incontinence. Drugs Aging.25: 541-549.