Primary Sphincter Mechanism Incompetence (PSMI)

PSMI is the most common cause of urinary incontinence in adult female dogs seen in primary care practice.¹
Incontinence in spayed female dogs previously was called hormone-responsive, or estrogen-responsive, incontinence. This occurs an average of 3 years after ovariohysterectomy in approximately 20 percent of female dogs neutered between their first and second heat cycles. In dogs spayed before their first estrus, the incidence is reported to be 9.7 percent.² In another report, 5.1 percent of bitches were found to have spay-related urinary incontinence.³ No association of increased risk to develop urinary incontinence was shown in a case control study of 202 incontinent female dogs neutered between 3 and 6 months of age.⁴ Female dogs neutered before 3 months of age, however, were shown to have twice the risk to develop urinary incontinence before 6 years of age compared to neutering when older than 3 months.⁵ The main mechanism for the development of urinary incontinence with PSMI has traditionally been attributed to low urethral closure pressure, though some dogs have a bladder component to this form of urinary incontinence.⁶ Urinary closure pressure is decreased 12 to 18 months following spaying in normal dogs,⁷,⁸ and it is speculated that this pressure continues to decline with age.

PSMI may occur in any breed of dog or in mixed breed dogs but some breeds are overrepresented, including the Doberman pinscher, Giant Schnauzer, Old English Sheepdog, Rottweiler, and Boxer. The German Shepherd and Dachshund are underrepresented in some reports of dogs with PSMI.⁹ Labrador retrievers were underrepresented in another study.¹⁰ PSMI is more common in large dogs (> 20 kg) in which the incidence of incontinence may be as high as 30 percent.¹⁰ Bitches weighing more than 10 kg were nearly 4 times as likely to develop post-spay PSMI than those less than 10 kg.⁴ Urinary incontinence can occur before spaying in some breeds, such as Greater Swiss Mountain dogs, Soft Coated Wheaten terriers, Dobermans, and Giant Schnauzers.

Adrenergic Treatment of PSMI

Phenylpropanolamine (PPA) is often prescribed as the initial treatment to restore urinary continence in dogs with PSMI by stimulating the alpha-adrenergic receptors along the urethra.¹ Phenylpropanolamine was found to have spay-induced urinary incontinence. Nearly all affected dogs have some improvement in continence after treatment with PPA. The largest dose should be given at night to control incontinence while the dog is sleeping. In dogs with incontinence only at night, dosing only at night can be effective. PPA may become less effective with prolonged use (so-called tachyphylaxis but decreased effectiveness over time could also be due to further decrement in MUCP). Occasionally, simply increasing the dosage of PPA is sufficient to regain control of continence. Pseudoephedrine was found to be an unsatisfactory alternative treatment to PPA for PSMI in dogs due to a combination of less urodynamic effect on urethral closure, lower continence scores, and more adverse effects.¹² Phenylpropanolamine can be used in the illicit manufacturing of amphetamines, so caution should be used to limit prescription of PPA to responsible owners for use in their dogs to treat PSMI. There are currently no federal DEA requirements for veterinarians to track their phenylpropanolamine sales.

Proin® (phenylpropanolamine hydrochloride; Pegasus Labs) was approved for use in dogs for treatment of PSMI as noted in the March 2012 FDA Register. Proin® is supplied in 25, 50, or 75 mg chewable tablets. The label dose is 2 mg/kg twice daily. Information about the effectiveness and safety of Proin is detailed in the FDA Freedom of Information Summary NADA 141-324. Proin® significantly decreased the mean number of urinary accidents per week compared to placebo. In a 28-day placebo-controlled study, loss of body weight ≥ 5.0 percent was reported as a side effect in 16.1 percent of PPA treated dogs (6.8% placebo group), compatible with its known appetite suppression effect in humans. Systemic hypertension was detected in 34.6 percent of dogs treated with PPA in an open 6 month clinical field study as noted on the Proin® label and in the NADA summary. Although systemic hypertension did not develop after months of PPA exposure to young dogs in an experimental setting, we have observed client-owned dogs with PSMI treated with PPA that have developed systemic hypertension. Eleven of 104 dogs with clinical signs related to overdose of PPA were reported to have systemic hypertension.¹⁴ Hypertensive retinopathy has been reported in one dog with PPA overdose.¹⁵ In one study of normal Beagle dogs, blood pressure increased as PPA dose increased (placebo, 1 mg/kg, 2 mg/kg, and 4 mg/kg every 12 hours for 7 days crossover pattern). The maximal increase in systolic, diastolic, and mean blood pressure was seen 2 hours following oral dosing of PPA. Heart rate was significantly decreased at 2 hours in dogs receiving 1 mg/kg and 2 mg/kg PPA, but
not for dogs receiving 4 mg/kg of PPA. Severe hypertension developed in isolated dogs of all PPA dose groups but was more commonly encountered in dogs with higher doses of PPA. There was no cumulative effect of PPA on blood pressure between day 1 and 7 but the possible development of a cumulative effect from PPA dosing given for weeks and months cannot be excluded. Restlessness and behavioral changes can be observed with or without evidence for systemic hypertension. Relative contraindications include known underlying cardiac disease, chronic kidney disease, or already-existing systemic hypertension. Increased thirst is also noted on the Proin label as a side effect. We recommend systemic blood pressure be measured before beginning PPA treatment and periodically thereafter to identify the development of systemic hypertension. Blood pressure should be measured 2 hours following administration of PPA based on the above observations in normal Beagles.

**Estrogen Treatment of PSMI**

Estrogens are an effective treatment for PSMI in many dogs and can be given much less frequently than PPA. Incontinence is controlled in 60–80 percent of affected dogs treated with estrogens alone for PSMI. Estrogen increases the sensitivity of urethral α-adrenergic receptors to catecholamines. Estrogens also may increase the number of receptors. The MUCP increased on the UPP after treatment with estrogens for a week in one study, but has not been measured in nearly as many studies as with PPA treatment. Diethylstilbestrol (DES) is dosed at 0.1–1.0 mg (0.02 mg/kg) per dog PO for 3–5 days followed by 0.1–1.0 mg PO every 3 to 7 days. DES has become more difficult to obtain because it is no longer used in human patients but it is available from veterinary compounding pharmacies. Premarin® (conjugated estrogens—obtained from pregnant mare’s urine) is dosed at 20 µg/kg PO q3d or q4d. This drug contains sodium estrone sulfate (50–65%), and sodium equilin sulfate (20–35%). Estrone is converted to estradiol. Although published information on the use of Premarin® in dogs with PSMI is lacking, we have had success with this product in our hospital. Oestradiol (Incurin®) is a naturally occurring, short-acting estrogen. Incurin is licensed for use in incontinent neutered female dogs as noted in the FDA Federal Register in December 2011 and in Europe since 2000). Incurin® is dosed at 2 mg per dog per day for 1 week followed by reduction to minimally effective daily dose (0.25 to 2.0 mg per dog per day) and finally alternate day dosing (dose not related to body weight) if urinary continence is maintained during dose reduction. In one study, 61 percent of dogs achieved continence and 22 percent improved for an overall response rate of 83 percent with oestriol treatment; no hematologic abnormalities were identified. Similar beneficial outcomes were shown in a series of dogs used to gain FDA approval in the USA for estriol treatment of PSMI to control estrogen-responsive urinary incontinence in ovariohysterectomyed female dogs (Freedom of Information Summary Original New Drug Application; NADA 141-435 Incurin [Estriol] Tablets Dogs Approved July 25, 2011). Potential complications of treatment with estrogens include induction of the clinical signs of estrus, perineal alopecia, and bone marrow suppression. We have not encountered bone marrow suppression in dogs receiving low dose intermittent estrogens. Bone marrow suppression is most often seen after use of long-acting injectable estrogens such as estradiol cypionate or with overdose. A recent abstract reported the 6-month safety of high doses of estriol given to young spayed female Beagles at 0, 2, 6, or 10 mg per dog per day. At 10 mg/day (5x increase over recommended daily dose) redness and swelling of the vulva, and vulvar discharge were noted as the most common findings. Teat enlargement was also occasionally noted. Details about bone marrow health in these same 24 dogs given the highest doses of estriol are provided in the NADA Summary. During the 6 months of this study for the highest dose of estriol, anemia did not develop in any dog, bone marrow aspiration biopsies were normal, and the myeloid:erythroid ratio was normal.

Clinical experience suggests that some dogs require both PPA and estrogens for optimal control of incontinence suggesting synergism of effect, though one study indicated that adding PPA to estradiol did not result in additional increases in urethral resistance. One report suggested that abnormal bladder storage function may be part of the pathophysiological mechanism in many female dogs with refractory urinary incontinence. Some dogs that fail to respond to PPA alone respond with the addition of flavoxate or oxybutynin. The injection of botulinum toxin into the submucosa of the urinary bladder of 11 dogs with PSMI resulted in urinary continence for most dogs averaging a 5-month effect. These findings suggest that bladder detrusor instability may complicate PSMI in some dogs.

**Non-Medical Treatments for PSMI**

Urethral bulking agents delivered through a cystoscope can be effective in the treatment of PSMI in dogs. Successful implantation of urethral bulking agents avoids the need for daily medication. The bulking agent and implantation process are expensive, require general anesthesia, and may not have long duration of effect in some dogs. Successful implantation requires special equipment and technical expertise. Submucosal urethral collagen injections improve continence in most dogs that have failed PPA treatment for PSMI. A 50–80 percent response rate
Ectopic Ureter(s)

Ectopic ureter (EU) is the most common anatomic abnormality causing urinary incontinence in female dogs and is far more commonly diagnosed than EU in the male dog. Based on two recent reports, male dogs may have more problems with ectopic ureter than previously appreciated.\textsuperscript{12,33} Ectopic ureter is diagnosed when ureteral openings terminate anywhere else than in their normal location in the trigone. Though ectopic ureter is often viewed as a simple plumbing bypass problem, it is at times more complex in that it can be associated with a short urethra, low urethral closure pressure (PSMI), and poorly described abnormalities in the formation of the urethra-vesicular junction. Abnormalities in the development of the kidney (single agenesis, renal hypoplasia) are encountered in some dogs as well as the finding of hydronephrosis and hydroureter. Urinary tract infection can occur in the lower urinary tract and also in the kidneys (pyelonephritis) due to the predisposing anatomical abnormality and effects of obstruction. So it is important to evaluate the entire urinary tract in those with suspected ectopic ureter(s).

Ectopic ureters are more common in certain breeds including Siberian huskies, Labrador retrievers, Golden retrievers, Soft Coated Wheaten terriers, Newfoundland, Welsh Corgi, and Poodles of any size. Detailed findings from young female Soft Coated Wheaten terriers with urinary incontinence are described in a recent report.\textsuperscript{34} Related Entlebucher Mountain Dogs affected with ectopic ureter(s) have been described both with and without urinary incontinence.\textsuperscript{35} Multiple reports document the diagnosis of EU in littermates, half siblings, and other related family members. As a note of clinical interest, the Doberman pinscher, another breed overrepresented with juvenile urinary incontinence is not affected by EU but instead by familial PSMI. It has been reported that a specific breed diagnosed with EU can affect the prognosis and outcome of surgical treatment. All 16 Labrador retrievers diagnosed with EU in recent study regained continence after surgical repair.\textsuperscript{32}

Bilateral displacement of the ureteral orifices is detected more often than unilateral. Early reports of primarily unilateral involvement likely were affected by limitations of imaging (i.e., lack of urethrocytoscopy). Termination points in those with bilateral EU may not be located at the same site (e.g., proximal and mid urethral; proximal and distal urethral). A diagnosis of ectopic ureter should be made if the ureteral orifice is displaced even minimally from its normal position in the trigone. Most ectopic ureters in female dogs terminate in the urethra after tunneling from more proximal locations.\textsuperscript{36} Ectopic ureters may have their terminal opening still within the bladder, at the vesico-urethral junction, proximal to distal urethra, and the vestibule. Extramural ectopic ureters have been reported rarely until recently.\textsuperscript{32}

Transurethral cystoscopy is the gold standard for the diagnosis of ectopic ureters in female dogs.\textsuperscript{36} A definitive diagnosis of ectopic ureter is made during urethrocytoscopy by visualization of additional openings in the urethra or vestibule. The ectopic ureter terminus point is classified as located at the vesico-urethral junction, proximal urethra, mid-urethra, distal urethra, in the vestibule, or still within the bladder but not in the usual trigone area. The ectopic ureteral openings in the urethra are always located dorsally or dorsolaterally as a consequence of the abnormal embryologic migration pattern.

Treatment of Ectopic Ureter(s)

Failure to adequately control urinary continence has plagued the success of all published surgical procedures to correct EU in female dogs. Surgical transposition of the ureter is helpful in controlling incontinence but post surgical incontinence occurs in at least 50 percent of affected female dogs.\textsuperscript{37,38} Improved continence (as high as 100%) has been demonstrated in several studies involving surgical and minimally invasive treatment of EU in male dogs.
Urethral bulking agents and AUS both help to control urine leakage by increasing the basal pressure of the urethra. Submucosal urethral collagen injections can be used with success in some dogs with ectopic ureters that continue to have urinary incontinence after conventional surgery. The use of urethral bulking treatment with collagen was reported in 5 female dogs following unsuccessful ectopic ureteral surgery. Urethral bulking was also used in 5 female dogs instead of surgery for dogs with proximally located ectopic ureters. The degree of urethral coaptation following collagen implantation was less complete in dogs with previous ectopic ureter surgery likely due to the effects of previous surgery and scarring making the submucosal injections more difficult.28

Endoscopic laser ablation of ectopic ureters has recently been reported as a minimally invasive procedure to reestablish the ureteral orifice(s) within the bladder at the trigone. The laser is used to ablate the intraluminal portion of the submucosal ureter creating a neo-ureterocystostomy in a more normal trigonal position. Continence was reported for a median of 18 months in 4 of 4 male dogs following laser ablation of ectopic ureter.39 In 13 female dogs that were able to be evaluated following laser ablation for ectopic ureter, 4 were completely continent without drugs, 5 were completely continent with drugs, and 4 improved on PPA but were still incontinent.40 Laser ablation of the ureteral remnant within the urethra is not expected to result in complete remission of incontinence in some dogs with ectopic ureters that have an associated PSMI. Female dogs with urinary incontinence alone (26 dogs), recurrent UTI alone (2 dogs), or both urinary incontinence and UTI (8 dogs) were recently reported.41 Thirty of these 36 dogs had concurrent ectopic ureter. Urinary continence scores improved and recurrent UTI was reduced following endoscopic laser ablation in 19 dogs with paramesonephric septal remnants, 11 with vaginal septa, and 6 with dual vagina.

For those with persisting incontinence following laser ablation or other surgical procedures, urethral bulking agents,28 and placement of an AUS45 remain options for further treatment. In 8 female dogs with ectopic ureter that had persisting urinary incontinence following ectopic ureter surgery or urethral collagen implantation, the degree of urinary incontinence improved following placement of an AUS.52 In 6 female dogs of another study that failed to gain continence following surgical repair (4 following neoureterocystostomy and 2 after laser ablation of intramural EU), placement of an AUS resulted in markedly improved continence in 5 of the 6 dogs.31