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Urinary incontinence in bitches after spaying

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List of abbreviations

ACh - Acetylcholine

BW - Body weight

FSH - Follicular stimulating hormone

GnRH - Gonadotropin-releasing hormone

LH - Luteinizing hormone

OE, OVE - Ovariectomy

OHE, OVH - Ovariohysterectomy

PPA - Phenylpropanolamine

UI - Urinary incontinence

USMI - Urethral sphincter mechanism incontinence

UTI - Urinary tract infection

1. Introduction

In my thesis, I will look into the problematic side effects that may occur following routine ovariectomy (OE) and ovariohysterectomy (OHE), in particular urinary incontinence in bitches. As this is a relevant question to be addressed in small animal veterinary medicine, it is important to me as I wish to work in this field and have particular interest for obstetrics. This is an issue, which is as relevant today as it was ten years ago. To this date, we do not know the complete pathophysiological background to urinary incontinence. Continuous research on this topic is done in both human and veterinary medicine. The differences between the traditions in spaying of dogs in Hungary and Norway, due to differences in animal welfare laws, are particularly interesting in regards to this topic. I will look into the background, treatment options, diagnosis and clinical relevance. My work is based on peer-reviewed articles, and I have worked on it as a literature review. In the end of my thesis, I will look into three case studies collected at AniCura Byåsen Dyrehospital in Norway, where I had my practice during the 11th semester, and one case from another student.

1.1. Goals

My goals in this thesis are to find out what predisposes bitches to developing UI, and in particular spayed bitches. Why do they develop incontinence, and who are more at risk? What advantages and disadvantages may be seen in regards to spaying and incontinence; is an important question for me. I would like to determine the most at-risk groups of bitches, and how we potentially might lower these risks. Moreover, I wish to find the best methods of therapy, and how these are applied in some practical examples by studying a few cases. I wish to evaluate the success of therapy and availability for the pet owners.

2. Spaying

Spaying results in the permanent cessation of reproductive function, and is a widely used method of contraception among pet animals. In bitches, there are two main surgical methods where the gonads are removed: ovariectomy (OVE) and ovariohysterectomy (OVH). These methods are performed via an incision through the linea alba or the flank, or via laparoscopy. Pet population control can in this way be achieved via surgical contraception, and is often the technique of choice. However, the timing of performing the gonadectomy in dogs and cats, and the necessity, is still controversial. The reason for this is that gonadectomy results in a mixture of benefits and adverse effects. Depending of the age at neutering, sex, species and breed, gonadectomy may affect the pet on various levels (Reichler, 2009). Normally, there are few intra- and postoperative complications in connection with the surgical intervention (Johnston et al., 2001).

2.1. Effect of spaying on the reproductive tract

With removal of the gonads, elimination of diseases directly connected to these tissues can be achieved. For example, we remove the chances of developing diseases like ovarian tumours and cysts, as the affected organs are no longer present in the body. At the same time, spayed bitches and male dogs are no longer susceptible to diseases mediated by sexual hormones, like uterine disease or benign prostatic hyperplasia. Uterine pathology does not exist in spayed bitches, but may on the other hand often be seen in intact bitches, and individuals treated with progestogen. The incidence of diseases such as pyometra is significantly decreased in countries where gonadectomies are routinely performed (Reichler, 2009). In Norway, by law, it is illegal to perform gonadectomy on healthy dogs for preventative measures. In accordance to the Law on Animal Welfare LOV-2009-06-19-97 § 9. “Medicinal and surgical treatments; surgical interventions and removal of body parts on animals without a warrantable reason should not be performed. Dehorning and castrations is allowed when it is deemed necessary in consideration to animal welfare or other special reasons.” (Translated from Lovdata.no, 2016). Accepted reasons for spaying dogs may for example be pyometra, pseudo pregnancy or extreme behavioural issues related to sex hormones. In all cases, a veterinarian must evaluate the given patient and decide what the best therapy option is.

2.2. Effect of gonadectomy on development of tumours

Mammary gland tumours are the most common form of tumours found in bitches, with chances for development in intact bitches believed to be between 2% and over 20%. We find evidence supporting breed predisposition, like in dachshunds and some poodle breeds. Besides genetic predisposition, gonadal hormones seem to influence the pathogenesis of mammary gland tumours. In bitches who are spayed, these types of tumours are very rarely seen. The age at which the dog is spayed, also plays a big role in regards to the decreased chances for developing mammary tumours. The risk of developing mammary tumours in bitches spayed before their first estrous cycle decreases by 99.5%. This is a high number, and a significant positive effect from the pre-pubertal paying. Bitches spayed after their first estrus, but before their second, has a 92% lower chance of developing malignant mammary tumours compared to intact bitches. Interestingly, studies have found that the sparing effect of the spaying seems to be lost, or reduced, after the second estrous cycle. Not only the number of cycles, but also the age of the bitch has an effect. It is believed that after reaching 2.5 years, the wanted sparing effect of spaying is also gone. However, chances of developing benign mammary tumours is still reduced even after the second cycle, or after reaching 2.5 years of age (Reichler, 2009).

Development of tumours in the reproductive tract of spayed bitches is generally rare. Most of the canine vaginal, vulvar and uterine tumours are leiomyomas. As these types of tumours were mainly seen in intact bitches, and not in individuals gonadectomised before 2 years of age, a hormonal background was suspected. Researches have also found evidence supporting the fact that performing an OVH at the time of tumour removal seems to be beneficial. A review was made by the researchers, which concluded that none of the dogs who underwent concurrent OVH suffered from relapsing tumours (Reichler, 2009).

2.3. Effect of spaying on external genitalia

The development of external genitalia occurs due to the influence of gonadal hormones. We can therefore understand that when performing a gonadectomy, and consequently lowering the amount of sexual hormones circulating in the body, the development of the external genitalia will be affected. The timing of the gonadectomy influences the size of the vulva of the bitch. We also know that the occurrence of recessed vulva, perivulvar dermatitis and vaginitis are higher in spayed bitches than intact dogs. Furthermore, the timing of spaying affects the incidence of these diseases; it is often higher in bitches who were spayed during

puppyhood. Vaginitis may occur as the so-called juvenile-vaginitis, or as a consequence of atrophy of vagina following gonadectomy. It is still discussed whether spaying of bitches with juvenile vaginitis may lead to persistent vaginitis, or even lifelong problems. Allowing these bitches to go through an estrous period may help in the resolution of juvenile vaginitis, but it is not certain what effects increasing age and maturation of the immune system will have on this disease (Reichler, 2009).

2.4. Effect of spaying on metabolism

Even though obesity may occur in both intact and spayed bitches, and due to various other reasons, we have data indicating that neutered animals have a higher risk of gaining weight (Reichler & Hubler, 2014). In cats, this has been proven with results from several studies. In dogs, the information is more conflicting. Population studies recently published indicates that neutering before 6 months of age lowers the prevalence of obesity. These results have raised questions on whether early spaying decreases the risk of obesity amongst spayed bitches. To this date, we do not have the proper answers to these questions.

What we do know, is that the obesity is not a direct consequence of gonadectomy, but due to lowered metabolic speed. Lowered metabolism is an effect of the spaying. A prospective study was made to compare the food intake and weight gain for 90 days after surgery in bitches who went through OHE, and in bitches who had laparotomy without OHE. The food intake was significantly higher in spayed bitches, and they had gained more weight after the surgery (Johnston et al., 2001). It is important to prevent obesity in these individuals, as well as in intact animals, to avoid diseases and health risks associated with obesity. Simple measure can be taken to avoid obesity, like feeding the dog with a proper diet and assuring a good level of physical activity.

3. Urinary incontinence

Urinary incontinence is the involuntary loss of urine during the filling, or storage phase, of the bladder (Reichler & Hubler, 2014). UI is frequently observed after the removal of ovaries in bitches (Veronesi et al., 2009). As a result, urine leaks when the animal does not intend to urinate. In the veterinary practice this is a common problem. It can be considered a welfare problem for the animal, as it may lead to lifelong conditions that require daily medical treatment. If the therapy is not successful, the incontinent animal might suffer from the condition, as well as it being a difficult situation for the owners to handle.

The consequences of dripping urine over a longer period of time are numerous. It may cause soaking of the area from the leaking urine, or soaking as a result of the bitch licking herself trying clean the urine off. Unfortunately, this often leads to rashes, infectious dermatitis and ulcers around the perineal area, causing pain and discomfort for the animals (Veronesi et. Al., 2009). It can also cause a greater risk of developing general infections. These lesions often require medical therapy in the form of antibiotics, and close attention and care. In addition to risks of developing cutaneous diseases, lower urinary tract infections may develop (Ponglowhapan et al., 2012). As the vulvar area is dripping urine, bacteria may aggregate in the area and cause an ascending infection. Persistence of urinary incontinence in a bitch also imposes sanitary and management problems for the owners. The therapy of incontinent bitches often requires extensive daily care and treatments, and great patience. Sometimes, euthanasia may be requested by the owners if they cannot manage the situation.

The type of UI we typically see after spaying is called Urinary Sphincter Mechanism Incompetence (USMI) (Reichler & Hubler, 2014). This term describes a functional weakness of the urethral closing mechanism, that is neither congenital nor juvenile. This condition is reported to be associated with OVH, and is sometimes called spay-incontinence. The underlying pathophysiological mechanism is to date not fully understood, but the therapy is usually successful (Kanca et al., 2012). It was earlier called Oestrogen-responsive urinary incontinence, as it was believed to be the decrease in oestrogen alone, which caused the incontinence (Johnston et al., 2001). The influence of hormonal changes after spaying is discussed, and is most likely one of the main reasons for incontinence occurring. Several other potential causes are also discussed to be in the background for development of USMI, like whether structural and functional changes to the bladder after spaying have an impact.

Differences between the techniques used during surgery; overiectomy or ovariohysterectomy, are also considered as possible reasons. However, after several retrospective studies, it is found that there is no difference between OVE and OVH and the predisposition to developing UI. Removal of the cervix has similarly been investigated as a possible increase of predisposition, without finding any correlations (Ponglowhapan et al., 2012). In most cases, the diagnosis of USMI is made on the basis of a detailed anamnesis, physical examination and basic tests such as urinalysis and urine bacterial culture.

Like already mentioned, the exact pathophysiological background for the development of USMI is not yet known, and a number of theories have been purposed. The reason why the urethra fails to maintain sufficient closure pressure may be due to various reasons; adhesion formation between the bladder neck and vaginal/uterine stamp, anatomical or neural damage, caudal positioning of the bladder with shortening of the urethra ("pelvic bladder"), or hormonal changes following the removal of ovaries (de Bleser et al., 2011). Some bitches start showings symptoms of incontinence relatively soon after the spay, whilst most dogs start showing symptoms years after. For this reason, it took a long time before the connection between spaying and UI was understood (Arnold et al., 2009).

3.1. Oestrogen effect

For many years it has been deliberated what role the decreasing oestrogen levels after a spay has on the incidence of urinary incontinence. It was believed to be the main reason for the development of UI after spaying. Today, this theory is no longer backed up to the same degree. We now know that bitches treated with gestagens to suppress the oestrous cycle do not have an increased risk of developing UI, even though their ovaries are suppressed and their serum oestrogen levels are kept at a basal level, too. Also, the plasma oestrogen levels of an incontinent, spayed bitch are approximately the same as an intact, continent bitch. After reviewing the improvements in incontinent bitches receiving daily oestrogen therapy it was shown that only 61-65% of them became continent again (Arnold et al., 2009). These facts point to the conclusion that the oestrogen levels alone cannot be responsible for the development of USMI.

3.2. Aetiology behind urinary incontinence

The aetiology of urinary incontinences is variable, and results of various conditions. Spaying is by far the only reason for urinary incontinence in dogs. Ectopic ureters, fistulas or urinary tract infections may for example also be in the background. The urinary incontinence is due to either an acquired situation, or a congenital dysfunction /anatomical defect. Furthermore, the UI cases can be categorized based on the aetiology of its occurrence: Neurogenic urinary incontinence and non-neurogenic urinary incontinence (Reichler & Hubler, 2014). Dogs with neurogenic urinary incontinence usually present with other signs of central nervous system dysfunction. Those individuals with non-neurogenic UI can further be divided into two groups: dogs whose bladders remain distended, and dogs whose bladders can empty completely, even though urine dribbles between micturition. Most dogs belong to the latter group (Reichler & Hubler, 2014).

Neurogenic urinary incontinence occurs due to nervous system damage leading to abnormalities of micturition. This is most commonly seen after trauma to cauda equina, or luxation of coccygeal vertebrae. If this causes lower motor neuron dysfunction, the animal will get an excessively dilated bladder termed as flaccid neuropathic bladder. Non-neurogenic urinary incontinence is the result of conditions not involving damage to the nervous system. This could be systemic diseases, administration of diuretics, congenital defects, intersexuality etc. (Ponglowhapan et al., 2012). This is where we find urethral sphincter mechanism incompetence as a cause of incontinence, very often as a result of spaying in bitches.

Incontinence develops when the resting pressure of the urethra is lower than the pressure in the bladder (Reichler & Hubler, 2014). As a result, urethral closure pressure in insufficient, causing subsequent urine dribbling. USMI often has this aetiology, and it is believed to be due to the hormonal changes after a spay. However, it could also occur in dogs with congenital USMI or urethral hypoplasia. This exemplifies the importance of a proper diagnosis.

Excessive intra-vesicular pressure can also result in urinary incontinence. This could happen due to involuntary contractions of the bladder, or in cases of bladder hypoplasia. In these cases, the pressure inside the bladder is higher than that of the urethra. This condition has to be separated from the so-called detrusor instability, which may occur in connection with any

inflammatory process in the urinary tract, or in case of neoplastic changes. Interestingly, the condition of detrusor instability may even be seen after gonadectomy. It is important to be aware that this can even be a consequence of spaying (Reichler & Hubler, 2014).

3.3. Making a diagnosis

The work-up of urinary incontinent patients may be challenging due to its complex nature. To facilitate the diagnosis, it is useful to differentiate UI associated with neurological signs, and non-neurogenic UI. When we meet the patient for the first time, it can be useful to make a neurologic examination to determine to which of these groups the patient belongs. We furthermore have to distinguish the "involuntary" loss of urine, from a behavioural problem. In the case of urinary leakage, dogs are not likely try to reach a place for urination, or take a micturition position. Urine dribbles from the animal involuntarily. This may occur at any time of the day, irrespective of the location of the animal. On the sofa, bed, floor etc. (Reichler & Hubler, 2014). The classical presentation of the incontinent patient is pooling of normal urine in areas where the dog has been sleeping (Johnston et al., 2001). In cases of behavioural problems, the dogs will in most cases take a micturition position. Additionally, a majority of dogs urinate in specific places in case of behavioural issues. The dog may for example be marking her territory at a specific place in the household.

When we have determined that the incontinence is non-neurogenic, and we have excluded behavioural problems, we need to examine our patient further. By looking at our patient data, especially the age, we might get ideas as to what may be potential and likely causes of the incontinence. If the bitch is relatively young, we must exclude congenital defects potentially leading to incontinence symptoms. The most common cause for congenital urinary incontinence is ectopic ureters (Chew & DiBartola, 2007). An ectopic ureter is defined as a urethral opening to the urinary tract at a location other than the trigone of the bladder, which is the normal location (Gültekin et al., 2015). Differentiation from this type of UI is therefore of great importance to veterinarians. At the top of the list of differentials in young dogs we also find inter-sexuality. This occurs rarely, but should be considered in young animals with UI (Holt, 2005). Dogs with ectopic ureters often struggle with urine leakage from the time of weaning. It is many times mistaken as a behavioural problem in connection with training the dog to become housebroken. Ectopic ureters are most typical in female dogs of certain high-risk breeds (e.g. Golden retrievers, Labrador retriever, Siberian husky, Soft-coated Wheaten terrier). The incontinence is usually nearly constant, and may

be associated with intermittent or persistent bacterial urinary tract infections. Ultrasound imaging can be helpful to diagnose the presence of an ectopic ureter, especially if it is dilated. Otherwise, we can use positive contrast vaginography and intravenous pyelography. These two methods are not suitable to visualize the end point of the ectopic ureter. To identify the termination-point the method of choice is urethrocystoscopy.

The next issue for the veterinarian is to differentiate UI from dysuria (painful urination) and polyuria (increased production of urine) (Reichler & Hubler, 2014). Dysuria could be a result of urinary tract infection, or other conditions causing pain during micturition. Polyuria due to polydipsia is often related to various hormonal diseases; like diabetes etc. It is not necessarily easy to tell if the dog is actually drinking too much, or too often. To diagnose polydipsia, we need help from the owners to estimate how much water the animal actually drinks. This can easily be measured. Water intake above 100 ml/day/kg body weight is considered abnormal. Healthy dogs generally consume between 50-60 ml/day/kg body weight, depending on moisture content of their food etc. (Schoeman, 2008). By instructing the owners to measure the water intake of the dog at home, we can get these numbers and evaluate them. In case of an excessive water intake due to an infection or hormonal problem, the owners often notice a change in the drinking behaviour of their dog at home. This is one of the most common causes for veterinary visits in the small animal medicine.

Like earlier mentioned, we have to keep the possibility of intersexuality in the back of our heads when examining incontinent patients. In particular, young incontinent dogs. Animals with intersexuality have female external genitalia. They have no true vagina, but instead a vulva. The vulva is in direct continuity with the urethra, and is called an urovagina. Intersexual animals often experience urinary incontinence, and should be kept on the differential list while examining the incontinent patient. A type of USMI can be found in these patients. With the help of vaginourethrography it can be diagnosed and managed, mostly with the help of medicines (Galav et al., 2004).

Bladder neoplasia may result in signs of dysuria, haematuria or urinary tenesmus, as well as urinary incontinence. Diagnosis of bladder neoplasia is usually made with radiography or ultrasound. The most common types of neoplasia found in the bladder is transitional cell carcinoma, leiomyoma and rhabdomyosarcoma. Surgical excision is possible; however not

always successful as long-term control is rarely achieved. Chemotherapy also has a limited role (Galav et al., 2004).

Cystitis will in most cases also cause urinary incontinence as a symptom. Cystitis is caused either by a bacterial infection or by urolithiasis. In cases where USMI is present, it can even lead to increased incontinence, enhancing the already present problem. Urine analysis and culture is recommended in case of incontinence to investigate the chances of a urinary tract infection. Antibacterial agent is selected on the basis of culture and sensitivity testing. Urethral tumours, on the other hand, do not typically present with incontinence signs, but it may occur. Especially in case of overflow, which can be seen if urethral obstruction is severe. Contrast radiography can be useful in making a tentative diagnosis. A typical clinical sign is irregularity of the urethral mucosa. The main differential diagnoses are urethral caruncles, and severe urethritis. Diagnosis can be made with the help of catheterization and biopsy. Treatment options are similar to those of bladder neoplasia (Galav et al., 2004).

Another reason for development of urinary incontinence, especially after spaying, is ureterovaginal fistulation. This can accidentally occur if the ureter(s) is accidentally incorporated into vaginal ligatures during ovariohysterectomy. Typical clinical signs in this case is that the animal feels unwell for a few days. Later, continuous dribbling incontinence develops as the ureters fistulate into the vagina. Diagnosis is made on basis of radiography. Surgery can be used for treatment, by anastomosing the ureters to the bladder (Galav et al., 2004). After looking at the numerous potential causes of incontinence, we can understand the importance of making a proper patient signalment and anamnesis to diagnose the incontinent patient.

4. History

The first time the connection between spaying and the development of UI was described, is about 50 years ago (Reichler & Hubler, 2014). It was seen as a rare side effect of spaying. Furthermore, it took about 20 years for the causal relationship and connection between removing the ovaries and development of UI was demonstrated. Neuronal damage as a side effect of the surgery was thought to be in the background for development of UI. This hypothesis has now been disregarded, as the incontinence does not occur until quite some time after the surgery. In addition, there is no difference in the risk of development of UI between OE and OHE (Arnold et al., 2009). Since then, it has been questioned about the connection between the age of neutering and the incidence of UI. Just a few years ago, this question was raised again by a systematic review of peer-reviewed original English analytic journal articles. The effect of neutering, or age at neutering on the risk of UI was studied. The overall conclusion was that the evidence is not strong enough to make firm recommendations on the age of neutering in connection with developing UI. However, this is till controversially discussed, and according to a population study, the spaying of puppies at ages lower than 12 weeks should be avoided as it may lead to an increased risk of development of UI. There were several other studies made. Some of them concluding that there is no correlation between age of surgery and the incidence of UI, and some concluding that there is a correlation. The latest study made on this topic, however, concluded that the factor, which is most decisive, is the weight (Reichler & Hubler, 2014).

5. Predisposition to urinary incontinence

Studies have proved that the chances for developing urinary incontinence after spaying is significantly higher than in intact bitches (Reichler & Hubler, 2014). The risk of developing UI in intact bitches and male dogs is low, between 0-1%. In spayed bitches the prevalence increases greatly to between 5% and 20%, and in some breeds of dogs even up to 60% (Coit et al., 2008). The dogs typically start showing signs of incontinence 2-5 years after spaying, but this can vary greatly. The spayed bitch may even start showing symptoms of incontinence almost immediately after the procedure, or up to 10 years after. This long time gap is the reason why understanding the connection between spaying and development of UI took such a long time. The average timing of the start of symptoms is set to 2,9 years of age, and represents the typical incontinent bitch (Ponglowhapan et al., 2012).

Incontinence affects the female dog population to a much higher degree than males (Coit et al., 2008). Gender differences associated with risks of developing UI may have to do with differences in anatomy, in particular the urethra. The female urethra is shorter than the male urethra. The striated urethral sphincter is also shorter in female dogs, and the contractile responses are poorer than those of the male dogs. This makes the female urethra and urethral sphincter more prone to lesions and abnormalities. Additionally, the prostate and colliculus seminalis, the prostatic part of the urethra near the entrance of the seminal vesicles, are believed to contribute to urethral resistance. Consequently, bitches are at much greater risk of developing urinary incontinence than the male dogs (Reichler & Hubler, 2014).

In comparison with urinary incontinence developing in women after birth, there seems to be no connection between the risk of UI and parturitions, or the number of pregnancies in dogs (Reichler & Hubler, 2014). Women can suffer from pelvic floor injuries during labour when delivering babies, leading to incontinence. Comparatively, dogs can suffer from muscle atrophy or damage of the muscles equivalent to the pelvic floor muscles. This can also occur in dogs who went through tail docking. The levator ani and coccygeus muscles atrophies and become damaged after tail docking (Reichler & Hubler, 2014). However, to date there has not been published any studies confirming the association between tail-docked and un-docked dogs, and urinary incontinence.

Studies were presented in an article showing their convinced conclusion that spaying and UI has a clear connection. One of the studies focused on the levels of gonadotropins in bitches with different risks of developing UI (Reichler & Hubler, 2014). 195 intact bitches and 310 spayed female dogs were used in the study, which concluded that 20% of the spayed female dogs presented with urinary incontinence for the first time after their spaying. Of the intact female dogs, only 2% were incontinent.

In addition to the spaying itself, a number of factors have been suggested to be in the background for developing USMI. Urinary incontinence is a multifactorial condition, and believably results from many different factors. Age, breed, body size, obesity, time of spaying, urethral length and bladder neck position, urethral tone, tail-docking etc. (de Bleser et al., 2011). A complex interaction between neuromuscular, vascular and passive elastic components are responsible for maintaining the urethral tone (Noël et al., 2010b). A discussion on whether early spaying predisposes to developing urinary incontinence is still going on, even though clear evidence is not yet found. There have been multiple studies made to research this topic; however, they have not concluded that this is a fact (Reichler & Hubler, 2014). Early spaying of bitches, before reaching 6 months of age, has many advantages. First of all, the surgery itself is easier to perform and has less traumatic effects. Secondly, it is more likely to prevent unwanted litters. Third, it has a great connection with lower the risk of developing mammary gland tumours. The age at spaying has been discussed, as it is believed by many to be a predisposing factor to UI.

Some breeds are more at risk of developing urinary incontinence. We see a higher incidence among Boxers, Rottweiler, Doberman, Irish Setter, Weimaraner, Springer Spaniel, Bobtail and Giant Schnauzer. These are larger breed dogs, with relatively high body weight. This confirms our theory that the body weight of the bitch is important. Studies show that the risk of developing urinary incontinence is increasing with higher body weight. However, some breeds of high body weight are not as susceptible to develop urinary incontinence; such as the German Shepherd and the Labrador Retriever. The theory on importance of body weight is therefore not always applicable (Reichler & Hubler, 2014).

5.1. Timing of spaying

Like already mentioned, differences in spaying before or after puberty was believed to have an impact on the development of UI, regardless of the actual age of the bitch. Today, however, this is not a confirmed theory. By the comparison of two studies from Switzerland, it was indicated that there is a lower risk of UI in bitches spayed shortly before puberty, compared to those bitches spayed shortly after puberty (Reichler & Hubler, 2014). It has been shown that the risk of developing urinary incontinence is twice as high if the bitch is spayed after her first estrus, compared to before. This was confirmed by another study of the same group of female dogs. During a large case study in England it was found that there is no difference in the risk of developing UI in case of spaying before or after the first heat. After the most recent study made on the topic, it was found that there is no clear connection between UI and age of spaying. It was, however, concluded that the weight of the animal is significant. Dogs with a body weight higher than 15 kg have seven times the chance of developing UI than the smaller breeds.

Interestingly, studies have also found that the timing of gonadectomy relative to the onset of puberty has an influence on the occurrence of UI during the day. 60% of early-spayed bitches showing signs of incontinence dribble urine not only while sleeping, but also while awake; while resting or out on a walk. On the other hand, those bitches spayed after their first heat are mostly incontinent during sleep (Reichler & Hubler, 2014).

6. Pathophysiology

Like mentioned earlier, the underlying pathophysiology of urinary incontinence occurring after spaying is not yet fully elucidated. The condition is multifactorial and has a complex pathophysiological basis (Nambiar & Lucas, 2014). However, we know about the many different simple underlying principles. By considering their pathophysiological conditions separately, and how they interact to change the pressure in the lower urinary tract, we have enough information to understand some possible causes of urinary incontinence occurring as a result of gonadectomy. Understanding the complex pathophysiology behind UI requires general information on the anatomy, physiology, neural control and biochemistry of the lower urinary tract.

We know that the intra-urethral pressure of the bitch decreases greatly after spaying, we even know that this occurs within a year after the surgery. When this pressure is reduced to a certain level, the bitch becomes incontinent. In addition to this, incontinence of the urethral sphincter may have an influence. The pathophysiology behind this is thought to be the early drop in oestrogen, and/or the secretion of GnRH, FSH and LH. The receptors of these substances are located in the lower urinary tract, but whether these changes after spaying is not known (Reichler & Hubler, 2014).

After gonadectomy we can see a lowering of the number of smooth muscle fibres in the lower urinary tract, and an increase in collagen fibres. This could explain the reduced muscarinergic excitability and contractility of the smooth muscle fibres in spayed bitches. The increase of collagen contributes to decreased conductivity of action potentials across the muscle cells (Coit et al., 2008). It has also been proved that, in contrast to pre- and postmenopausal women, the ratio of collagen-II to collagen-I in un-spayed and spayed bitches is similar. Recently it has also been shown that there is a reduced amount of glycosaminoglycan in the lower urinary tract of spayed bitches. This may cause a hyperactive bladder, potentially leading to urinary incontinence (Reichler & Hubler, 2014).

Prostaglandins, produced by cyclooxygenase enzymes throughout the body, may possibly play a role in the reflex of micturition. Both the receptors of prostaglandins, and their enzymes; cyclooxygenase, are less expressed in the lower urinary tract of spayed bitches (Reichler & Hubler, 2014). This can potentially influence the lower urinary tract in such a

way that incontinence occurs. More studies on this particular aspect would be necessary in understanding the role of prostaglandins and cyclooxygenase in the pathophysiology of USMI.

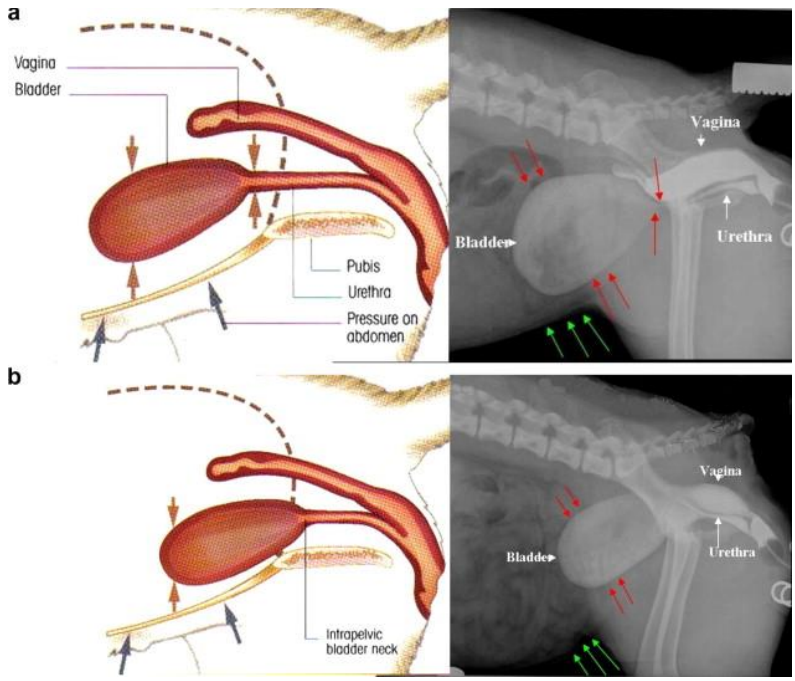

Figure 1: Difference in abdominal pressure exerted on the bladder and urethra in an intra-abdominal position (a) and an intra-pelvic position (b) (Noël et al., 2010b).

Furthermore, after spaying the bladder moves to an intra-pelvic position. The term pelvic bladder is defined as when more than 5% of the bladder length is located inside the pelvis. When examining a number of incontinent bitches with radiography, it was found that many of them have a pelvic bladder. In connection, they also have a shorter urethra. This caudally positioning of the bladder interferes with the pressure effect on the bladder and the urethra, and may influence the incontinence. As the urethra is moved caudally, into the pelvis, it no longer receives the same intra-abdominal pressure that normally helps to maintain the continence and avoid urine from entering the urethra (Noël et al., 2010b). When studying pictures illustrating the movement of organs of the urogenital system following spaying (Figure 1), and in particular the bladder, one can understand the role of the abdominal pressure on the bladder and maintenance of incontinence.

7. Physiology of the bladder

The main purpose of the urinary bladder is to receive urine from the kidneys and store it until micturition. Under physiological conditions, the components of the bladder and bladder neck potentiate and maintain the ability of continence and normal voiding cycles. Structurally the bladder is made up of interwoven fibres of detrusor muscles that form the body of the urinary bladder. Within the detrusor muscles there are specialized smooth muscles that originate from an embryological source. On the internal side of the muscle layers, the urothelium is functioning as a protective layer. It is distensible along with the bladder muscles, and forms an effective blood-bladder barrier to prevent uraemia (Nambiar & Lucas, 2014).

The interstitial cells are located deep to the urothelium (Nambiar & Lucas, 2014). These have recently been suspected of being the cells responsible for the "pace-making" activity of the bladder. Two groups of interstitial cells have been distinguished; sub-urothelial interstitial cells (myofibroblasts) and intra-detrusor interstitial cells.

7.1. Neurophysiology of the bladder

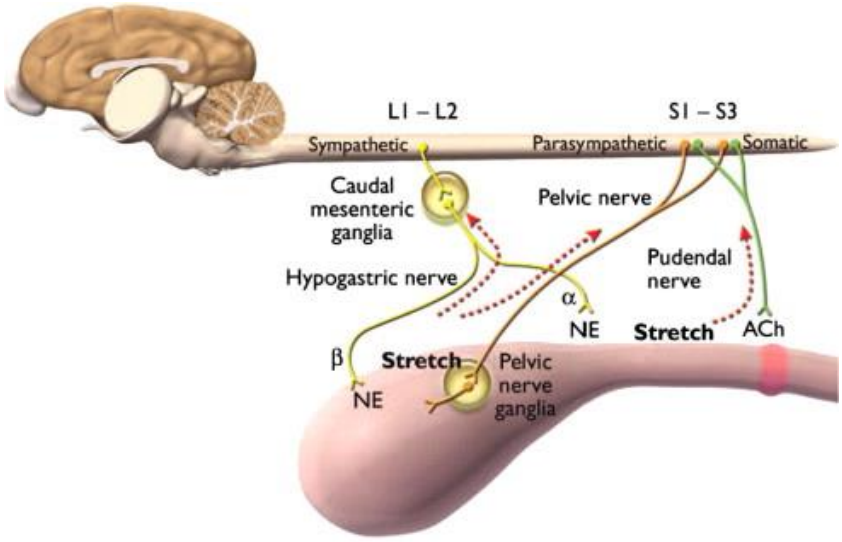

Figure 2: Innervation of the bladder; autonomic and somatic (Noël et al., 2010a).

The bladder is innervated and influenced by all the three nervous systems: sympathetic, parasympathetic and somatic. Sympathetic nerves innervating the external urethral sphincter release the neurotransmitter noradrenalin. Excitatory alpha-adrenergic responses resulting from sympathetic innervation, give an increased muscular tone and outlet resistance. There is also evidence of a sympathetic reflex initiated by bladder stretch, resulting in the

stimulation of beta-adrenergic receptors in the detrusor enhancing bladder relaxation and inhibiting parasympathetic stimulus. The parasympathetic nervous system influences the bladder by innervation of detrusor muscles, and releasing the neurotransmitter ACh, which consequently stimulate the muscles (Nambiar & Lucas, 2014).

Micturition occurs when the sympathetic innervation is inhibited, and consequently a relaxation of the urethral sphincter follows (Nambiar & Lucas, 2014). In this way, a small amount of urine enters the urethra. Via spinal reflexes and somatic/supraspinal mechanisms, further reflex bladder contractions are initiated. Simultaneously, parasympathetic excitation occurs, augmenting sphincter relaxation and contraction of the smooth muscles in the bladder. This leads to a higher pressure in the urine bladder and consequently expulsion of urine.

In most bitches, these physiological mechanisms work without problems. In the spayed bitches, something causes problems in these normal filling and voiding cycles leading to urine dripping. Especially loss of urethral pressure, or high bladder pressures due to abnormalities, leads to urinary incontinence.

8. Therapy

In cases where UI is considered a small problem, therapy might not be necessary. The problem may even never arise if the dogs is kept outdoors, for example in the garden. In households where the dog is kept inside, the incontinence may be a great problem for both the dog and the owners. We know from experience that the medical therapy of urinary incontinence is usually very effective. There are few side effects, and the patients are mostly using the same drug for the rest of her life (Reichler & Hubler, 2014). To be able to give the appropriate therapy to our patient, we have to rule out other diseases or causes that might cause urinary incontinence. Like mentioned earlier, there are multiple reasons which may be in the background. Additionally, a urinary tract infection may be present in an already incontinent bitch, increasing her symptoms. Knowing this, we always take a urine sample from our patient. A full urinalysis is run, and in some cases bacteriology. If we can be certain of the diagnosis, we can provide a better and more effective therapy.

Medical therapy is always the method of choice and should precede surgical therapy (Kanca et al., 2012). In most cases, medicinal therapy is successful and renders the patient symptom free. If not, we have to consider trying a different drug or surgical interventions. The type of therapy also depends on the owners, and what they wish to do in the situation. Two classes of drugs are commonly used in the therapy of USMI, namely alpha-adrenergic agonists and oestrogen compounds. Alpha-adrenergic drugs mimic the activity of the sympathetic nervous system. Their use is limited by the available drugs on the market and their legality in the given country (Ponglowhapan et al., 2012).

Usually, the dog must remain on medication for the rest of her life. This is the biggest concern regarding the therapy of incontinence; it requires life-long treatment. Owners often have to administer this medicine to their pet two or three times per day. Challenges may arise in connection with this, but oral administration of drugs should not be a major problem in dogs (Ponglowhapan et al., 2012). At the start of medicinal therapy, we can expect to see effects within relatively short time. Owners may in most cases notice an improvement within 48 hours after starting the therapy. A positive outcome of the therapy should therefore be easily recognized within relatively short time. If the given medication does not have the expected and wanted effect, it is easily possible to try one of the other medicines on the market, or a combination of different medicines.

Alpha-adrenergic agonists are the first line drugs in therapy of USMI (Reichler & Hubler, 2014). The meaning of agonist is a chemical substance that binds to a receptor to produce a biological response. They stimulate the smooth muscles comprising the internal urethral sphincter. The alpha-adrenergic receptors expressed in the internal urethral sphincter are stimulated by the drugs. Leading to a higher urethral closure pressure, it consequently helps in the treatment of incontinence. The two most used pharmaceuticals are Phenylpropanolamine and Ephedrine. The success rates of these medications vary; Phenylpropanolamine has 86% to 97% success rate, whilst Ephedrine has 74% to 93% (Reichler & Hubler, 2014). According to the study comparing the effects of the two, it became evident that the results from using Phenylpropanolamine is superior to the other.

8.1. Phenylpropanolamine (PPA)

The currently recommended dosage and rate of administration of PPA in incontinent dogs is 1-1.5 mg/kg bodyweight, every 8-12 hours (Reichler & Hubler, 2014). The drug is easily accessible, and sold at the pharmacy at a cheap price. Unfortunately, we might sometimes see a recurrence of the incontinence after a prolonged administration of PPA, or in dogs treated multiple times per day. It is proposed that this is due to desensitization of the alpha-adrenergic receptors in the urethra (Kanca et al., 2012). It is therefore assumed that it is advantageous to administer once daily instead of several times per day.

The sympathetic nervous system generates 50% of the urethral closure pressure, and thereby contributes to maintaining continence in the dog. The wanted effect from PPA, which is a sympathomimetic drug, can be explained by this fact. PPA works on the alpha-receptors in the smooth urethral musculature. Alpha-receptors are divided into two subgroups: alpha1- and alpha2-subtypes. These are distributed throughout the body in different tissues. Alpha1-receptors are mainly found in the target organs of the sympathetic nervous system. Alpha2-receptors are mostly found in neuronal synapses, and not in the target organs of the sympathetic nervous system. Today we know that the receptors found in the bladder neck and proximal urethra, which are responsible for maintaining continence in bitches, belongs to subtype 1. Phenylpropanolamine is a selective alpha1-agonist. The older substance, Ephedrine, is not as selective to subtype 1 and also stimulates beta-receptors. For this reason, we are more likely to see side effects in connection with Ephedrine. As a result, Phenylpropanolamine is considered the first choice medicine (Arnold et al., 2009).

Phenylpropanolamine produces a greater urethral closure pressure, thus inhibiting incontinence to a greater extent (Reichler & Hubler, 2014). At the same time, the side effects are less commonly observed. For this reason, the medicine is often used, as it is considered relatively safe for the patient. Side effects could be observed in some cases, but they are very rare. Sometimes, we might for example see gastrointestinal irritation, anorexia, nervousness, aggressiveness or apathy (Reichler & Hubler, 2014). These side effects are, however, not as pronounced in animals as they are in humans. In humans, the medicine is used to reduce the swelling of mucous membranes, especially those in the upper airways. It is a useful tool in the treatment of allergic and vasomotoric rhinitis in humans when local therapy is not sufficient. The side effects occur in more than 1/100 of humans. Side effects typically involve the airways: dryness in nose and mouth. Additionally, it can affect the central nervous system leading to sleeplessness, nervousness and drowsiness, as well as micturition problems (Felleskatalogen, 2014b).

Figure 3: PPA in the form of Propalin syrup (vet-medic, no date)

PPA has a good oral absorption, which is preferred for treatment of patients in veterinary medicine, and a bioavailability of 99% (Rinexin, 2016). Maximal plasma concentration is reached after 55 minutes with an immediate release solution, and in two hours with a sustained solution. Elimination of the drug from the body occurs mostly via the urinary tract untransformed. In the dog the half-life of the drug ranges from 3.5 to 5 hours, depending administration route (Noël et al., 2010b). These characteristics together with the safe

character of the drug, makes Phenylpropanolamine a good therapeutic agent for the small animal practice.

A study was made to evaluate the efficacy and the safety of long-term administration of PPA. 1.5 mg/kg BW PPA was administered once daily in the treatment of spayed incontinent bitches. This was compared to treatment three times per day with 1.5 mg/kg BW PPA tablets. Twenty-two spayed bitches suffering from urinary incontinence were selected for the study. Exclusion method was used to remove the bitches having UI as a result of other reasons, such as urinary tract infections, polyuria/polydipsia due to hormonal diseases, and behavioural reasons for inappropriate urination. Therefore, all the animals were clinically examined, urinalysis was performed and a thorough anamnesis was made (Kanca et al., 2012).

Before starting the therapy, a transabdominal ultrasonography was made to exclude any congenital abnormalities resulting in incontinence. Cephalic blood samples were made to evaluate complete blood count and haematology. If the results showed abnormalities, the animal was excluded from the study. Sterile urine samples were taken via cystoscentesis, for urinalysis and bacteriological culturing. The dogs included in the study showed no signs of urinary tract infections, or other abnormalities. All the dogs in the study were also scored on the basis of degree of UI experienced. The score was made on day 0 to evaluate the treatment outcome. Scoring was made on the basis of frequency of unconscious urination, and the volume of urine produced (Kanca et al., 2012).

The bitches were randomly allocated into one of two groups. In one group, the bitches received a PPA at the dose rate of 1.5 mg/kg once daily. The other group was given 1.5 mg/kg PPA three times daily. PPA was given orally in the food for 28 days. In dogs who became continent within 28 days, the therapy continued for 12 months. In bitches where the PPA therapy during 28 days was insufficient or unsatisfactory, the therapy was combined with oestriol for 14 days (1 mg/dog PO). No other treatment was permitted for the duration of the study. Both the owners and the veterinarians observed side effects during the study. Possible side effects were discussed with the owners, making them aware and fit to observe them (Kanca et al., 2012).

The frequency and amount of involuntary urination was analysed on day 7, 14 and 28 during the first month of the study. Thereafter, it was monitored once a month. In order to claim efficacy, the treatment with PPA had to improve the incontinence, and cause a lower amount or frequency of involuntary urination. Consequently, the response to the treatment was defined as a cure (continent), improvement (better total score), or no improvement (no change in the total score). Similar criteria were applied to the dogs receiving both PPA and Oestriol on days 0, 14 and 21 (Kanca et al., 2012).

Of all the dogs included in the study, three were unable to continue after 28 days. However, the clinical data from these three dogs were included in the statistical analysis. The mean age of the bitches included in the study was 6.05 +/- 2.30 years. The mean duration of time between start of participation in the trial and performed ovariohysterectomy (OHE) was 2.80 +/- 1.43 years. The average weight of the bitches included in the study was 28.68 +/- 7.8 kg. In the study, there were thirteen breeds included. Among these; Boxer, German Shepherd and Golden retriever, were represented with more than 1 individual (Kanca et al., 2012).

Results from the study showed that the mean length of time between OHE and the onset of UI in this study (2.80 +/- 1.43 years) is similar to earlier published findings. The age at which bitches started showing incontinence symptoms, however, was later in this study (6.05 +/- 2.30 years) than what has been described earlier. Previous studies have suggested that there is a connection between body weight and incidence of UI. This was confirmed by this study as well, where the bitches weighed approximately 28.68 kg on average (Kanca et al., 2012). In earlier studies, it has been reported that bitches with a body weight lower than 20 kg have a 5.1 % chance of developing USMI, whilst bitches with body weights above 20 kg reached 12.5 % chance of developing USMI (Ponglowhapan et al., 2012).

The larger sized breed dogs are said to be more predisposed to developing UI after OHE. Some breeds were predominant in this study: Boxers, German Shepherds, and Golden Retriever. Among these, Boxers and German Shepherds were reported to be at high risk. From both the treatment groups in this study; eight bitches became continent within 28 days of the study. These success rates are comparable to earlier results, even though the results were lower than in some studies. The reason for this is probably that the treatment was regarded successful only if the bitches became continent, and not if they had improvement (Kanca et al., 2012).

Furthermore, the result of this study proved that a single dose of PPA daily is sufficient to gain continence. It is also much more convenient for the owner and the dog, as well as it is a cheaper option. In this study, two of the dogs receiving multiple PPA doses became refractory to treatment. It is suggested that repeated PPA administration may lead to desensitization of the alpha-adrenergic receptors in the urethra. There are no studies made to evaluate whether reoccurrence of incontinence occurs in long-term treatment with PPA. However, it is assumed that administration of PPA once daily can prevent recurrences (Kanca et al., 2012).

The observed side effects and their severity were similar to previous studies. From group 1 three dogs has side effects, and six of the dogs from group 2 also experienced side effects. This division between the groups was like expected. However, the difference was not significant. The reason for this is most likely that only a small number of animals were included in the study (Kanca et al., 2012).

Even though most of our patients are good candidates for PPA therapy, we cannot use these drugs for all patients. When using selective alpha-adrenergic drugs, such as PPA, side effects may occur. This is due to the presence of alpha-receptors in other tissues than the bladder, such as the blood vessel walls. In humans, treatment with PPA or similar products, often lead to high blood pressure, headaches, and could even cause a stroke (Arnold et al., 2009). In dogs, however, this is not a common side effect, and is very rarely observed when using the recommended medicinal dose. PPA administered at an appropriate dosage in dogs more commonly causes self-limiting side effects like diarrhoea, vomiting, anorexia, apathy, nervousness and aggressiveness. In contrast, it has been proven in earlier studies that a decreased heart rate because of increased venous pressure, consecutive to PPA therapy, has been observed. As the arterial blood pressure was not monitored during this specific study, there were no similarities observed. Due to the knowledge we have about these possible side effects with PPA, it is recommended to perform serial blood pressure measurements in patients treated with alpha-adrenergics (Kanca et al., 2012). These side effects are some of the reasons for the importance of having other drug choices for therapy.

In 62.5% of the cases, a treatment with oestriol together with the PPA was effective. As oestriol is a naturally occurring oestrogen, it is currently the substance of choice for this type of therapy in bitches. The effect of oestrogen compounds is that it indirectly increases the

sensitivity of the alpha-adrenergic receptors to endogenously and exogenously produced catecholamine. This consequently leads to an increased urethral closure pressure. Therefore, it is reasonable to combine alpha-adrenergics with oestrogens for an optimal therapy, to get their synergetic therapeutic effect (Reichler & Hubler, 2014). In postmenopausal women, administration of both alpha-adrenergics and oestrogens together have shown to have a superior effect to using oestriol alone. Investigations on these drugs in dogs and cats is on the contrary very rare (Kanca et al., 2012).

The study concluded that PPA therapy is an efficient and cheap treatment option. Once daily with a dosage of 1.5 mg/kg bodyweight is optimal. It was also found that recurrence of incontinence often occurs in case of long time therapy with PPA. In combination with PPA, oestriol can be effective in those patients not responding to PPA therapy or those becoming incontinent after long time PPA therapy (Kanca et al., 2012).

In castrated male dogs, however, the positive results of such treatment with Phenylpropanolamine have not been seen as successfully as in spayed bitches. It has been estimated to a 44% success rate (Reichler & Hubler, 2014).

8.2. Oestrogen therapy

Even though most incontinent patients respond well to the PPA therapy, it is not always successful. For these patients, it can be an alternative to combine Phenylpropanolamine therapy with another drug. Like mentioned earlier, oestrogens can be used successfully together with alpha-adrenergic agonists (Kanca et al., 2012). They potentiate their effect in spayed bitches by sensitizing the alpha-receptors. In addition, studies performed in women and rats have shown that oestrogens can increase the bladder capacity and stimulate cell proliferation. Treatment with oestrogens is successful in 65% of the cases (Reichler & Hubler, 2014). The success rate is lower than that of PPA, which is one of the reasons why PPA is chosen as first line drug by many veterinarians. This is however, affected by the routines of the veterinarians. We can see that veterinarians who are used to prescribing oestriol continue using this drug, without trying the first line drug; PPA.

Applying oestrogens alone can be a successful therapy of choice, as well. Oestriol is a short term acting oestrogen medicine, which is often used for the therapy of urinary incontinence bitches. As dogs suffering from USMI have to be treated for the rest of their lives, it is a

positive fact that oestriol rarely cause any signs of bone marrow suppression. This is probably due to its fast working oestrogen effect in the body. Oestriol does not accumulate in the body tissues, even after long time repeated administration. This makes it a good medicine for the use in small animal practice (Felleskatalogen, 2014a).

Using long-acting oestrogen preparations for medical therapy may induce serious side effects. It can even lead to bone marrow suppression (Reichler & Hubler, 2014). Luckily, this occurs very rarely as the use of oestrogens is limited due to the increased risks of side effects. Long-acting oestrogens should therefore be used with great caution. Its indication is close to non-existing in the small animal practice. This is the reason why we only use short-acting oestrogens for the therapy of spayed bitches in veterinary medicine. An example of a possible oestrogen derivate that can be used is the previously mentioned Oestriol.

A study was made to evaluate the accumulation and the effect of per orally administered oestriol tablets. The study was performed during seven consecutive days, while giving the dogs 2 mg oestriol tablets once daily. The results showed that no accumulation occurred, leading to lower risk of side effects. With a 65-83% success rate, it proved that oestriol can help in the therapy of urinary incontinence. It can even be applied together with alpha-adrenergic agonists to potentiate their effect (Reichler & Hubler, 2014).

Although the more serious side effects often observed in connection with oestrogen therapy are not typically seen with oestriol, other unwanted symptoms may arise. Possible side effects of using oestriol compounds are typically oestrous signs, like swelling of the vulva and attracting male dogs. This can be problematic for the bitch herself, and also for the owners that have to manage this in the household. Using oestrogen preparations in bitches that are not spayed, should be avoided and carefully evaluated. These dogs may be subject to uterine bleedings, pyometra and possible other uterine diseases (Reichler & Hubler, 2014).

In conclusion, oestriol can be used safely for the therapy of USMI. On the other hand, we have alternative medicines with higher success rates and lower risks of side effects, like PPA. Oestriol is a valuable drug for the patients not responding well to PPA, or in countries where PPA might not be available for therapy.

8.3. GnRH therapy

Spaying not only results in a decreased urethral closure pressure within 1 year following gonadectomy, but also leads to a higher level of gonadotropins circulating in the blood. When the ovaries are removed during surgery, the dog loses the ability to give negative feedback to the hypothalamic-pituitary system. Consequently, the pituitary gland produces excessive amounts of the gonadotropins LH and FSH. The result is chronically elevated gonadotropin levels in the blood plasma (Donovan et al., 2014). Whether these elevated concentrations of hormones circulating in the blood have an effect on the occurrence of incontinence in spayed bitches is discussed, and it is believed to be a contributing factor.

Receptors for LH are found throughout the urinary tract. It has been postulated that the increasing amount of gonadotropins may play a role in the development of USMI in bitches. It is possible to downregulate the LH and FSH secretion by the pituitary gland with the help of long acting GnRH analogues. Bitches with long acting GnRH agonists can downregulate the LH secretion for prolonged time periods, and temporarily restore continence in incontinent bitches for varying durations. Studies made based on this showed various results. One showed a range from 50 to 738 days and another from 70 to 575 days. In comparison to the other treatment alternatives, GnRH agonists are not completely effective. However, unlike with PPA therapy, no adverse effects have been reported from using GnRH agonists (Donovan et al., 2014).

The only GnRH agonist developed for use in animals is Deslorelin acetate (Suprelorin). Other human medicines could also be used, but these are significantly more expensive (Donovan et al., 2014).

Other methods have been reported to temporarily decrease the LH concentrations and therefore may also treat USMI. Immunization against GnRH is one of such. This immunization elicits the synthesis of GnRH-neutralizing antibodies, which prevents GnRH from binding to the GnRH-receptors. Consequently, they prevent the synthesis of LH. In 2004, a commercial GnRH-vaccine was launched in the United States. The vaccine was labelled for use in male dogs, for the treatment of benign prostatic hyperplasia. For effective treatment, revaccination every 6 months was recommended. In addition, GnRH-vaccines have been shown to decrease testosterone in intact male dogs for approximately 20 weeks. It can also be used to terminate pregnancy in bitches safely (Donovan et al., 2014).

A comprehensive study has been made to determine the effectiveness of GnRH-vaccines. It was questioned whether immunization with GnRH would maintain continence in incontinent ovariectomized bitches, and whether it controlled USMI as well as PPA. The hypothesis was that GnRH immunization would maintain continence for a prolonged duration, and that it would be as effective as PPA. 60 ovariectomized bitches were enrolled to the Oregon State University´s Veterinary Teaching Hospital for this study. Urinary incontinence had been diagnosed using veterinary medical records. All the bitches recruited for this study were treated with PPA to maintain continence, receiving various dosages prescribed by the veterinarian. All the bitches taking part in the study were examined, and clinical health confirmed with various laboratory tests (Donovan et al., 2014).

The bitches taking part in the study were divided into two groups; novel-treatment dogs, and standard-treatment dogs. The first group of bitches, the novel-treatment dogs, were injected with 1 mL Canine Gonadotropin Releasing Factor Immunotherapeutic subcutaneously over the later thorax. 4 weeks later, they received one more immunization. The second group of bitches, the standard-treatment dogs, received 1 mL saline over the later thorax. They received one more injection 4 weeks later. Side effects from the injections could be observed in the participating dogs. One of the novel-treated dogs had tachypnea for 24 hours after the immunization. Another dog showed impaired movement because of soreness for 1 week after the initial treatment. Both these dogs were excluded from further study (Donovan et al., 2014).

During the study, blood samples were collected from the standard- and novel-treatment dogs before each treatment. Blood sampling was repeated at 6, 8, 10, 12, 16, 20 and 24 weeks after initial vaccination. 2 weeks after receiving their second immunization, the novel-treatment bitches stopped using PPA medicines. The group of standard-treatment bitches did not get PPA throughout the duration of the study. The owners registered and reported any incidence of incontinence before treatment, and for the duration of the study (Donovan et al., 2014).

For measuring the levels of GnRH antibody titres, serum samples were used. ELISA technique helped the process. In order to determine the LH concentrations, plasma samples were used, with the help of ELISA. By applying the Fisher´s exact test, the serum antibody

titres of GnRH from the two groups, novel- and standard treatment bitches, could be compared. Similarly, the novel- and standard treatment groups´ LH concentrations were compared using PROC MIXED in SAS. LH concentrations were compared by statistical analysis using the method PROC MIXED in SAS statistical software. Incontinent episodes before initial treatment, treatment with PPA, and treatment with vaccines was also compared using the PROC MIXED in SAS (Donovan et al., 2014).

Between the two groups of bitches, there were no differences concerning body size, age of the bitch, body weight, age at OE, or the interval between OE and the starting point of incontinence. This was ensured to make the two groups of the study as identical as possible, and thereby giving results that are more reliable. The clinical health of the bitches involved in the study was monitored with the help of blood biochemistry and haematology, urinalysis and urine culture. Throughout the course of the study all the bitches were in good health. Of the nine novel-treatment dogs in the study, four became incontinent again after a 14-day period of time. Therefore, they received a third immunization. Luckily, the bitches remained continent after his additional vaccination, and did not show periods of incontinence later (Donovan et al., 2014).

Out of the five standard-treatment dogs who were receiving PPA during the study, all five of them remained continent throughout the length of the study. Episodes of incontinence were compared, and it was concluded that there were significantly less accidents in the bitches treated with PPA, or the vaccine, compared with before any treatment was initiated (Donovan et al., 2014).

Before vaccinations started, all dogs in the study were negative for GnRH-antibodies. Bitches from the standard-treatment group were seronegative throughout the course of the study. All the bitches in the novel treatment group developed antibodies, which had a peak on week six. By the end of the study, they could still measure antibody titres in all bitches, but one. When looking at the result for plasma LH concentrations, one could see that at week 0, all bitches had levels at 5.06 +/- 1.99 ng/mL. All the bitches in the novel-treatment group showed plasma LH at basal level after GnRH immunization. On the other hand, the LH levels of the standard-treatment group was significantly higher (Donovan et al., 2014).

As the development of USMI is a common problem among spayed bitches, and treatment with PPA alone is not efficient in all individuals, it is important that we try to find alternative therapy methods. In this study, it was reported that GnRH immunization was able to maintain continence in four out of nine incontinent ovariectomized bitches for 14 weeks or longer, with an efficiency comparable to PPA. However, side effects due to the vaccination was observed in ten out of eleven vaccinated bitches (Donovan et al., 2014).

Due to the fact that three of the bitches were still continent at the time point of ending the study, a conclusion to the length of duration of the desired effect from the GnRH vaccine could not be made. From previous research made with castrated male dogs, it was shown that the levels of antibodies in the plasma were insignificant twenty weeks after the initial immunization. A fact, which definitely points to the conclusions that the vaccine had lost its initial effect, is that the testicular volume returned to the same as before the start of the study. It is therefore necessary to say that the study was unable to create an accurate image on how long we can expect the GnRH vaccine to be effective (Donovan et al., 2014).

The study, however, concluded that the GnRH vaccination effectively maintained continence in four out of the nine bitches. The vaccination was comparable to the PPA therapy in these dogs. Today, the vaccine is not available on the commercial market. This is due to the low product sales, which brought the product off the market (Donovan et al., 2014). Efforts should be made to make this vaccine available again on the market, as an option for treatment of USMI. It was proven that there is a positive effect made by the vaccination, and it may be a necessary treatment option for many of the USMI patients in the future.

Other groups of medications can also be used for treatment of UI. Subcutaneous GnRH implants have been used for therapy in bitches where the alpha-adrenergic therapy was not successful, had serious side effects, or where its application was contraindicated. In the bitches tested, about 50% has successful outcome of the therapy. In regards to side effects, there have not been any reports in spayed bitches using GnRH analogues. GnRH analogues may also be used in incontinent male dogs, as well as spayed cats. Furthermore, patients not responding to either alpha-adrenergic or GnRH treatment can use a combination of the two (Reichler & Hubler, 2014).

8.4. Other medicinal options

In human medicine, there is intensive research ongoing about the topic of UI, as so many humans struggle with this condition. Some drugs used in human medicine affecting the bladder can also be used successfully in dogs. A group of drugs called anticholinergics can be used for this purpose. These drugs block the neurotransmitter Acetylcholine. Some of the drugs within this group stabilizes the bladder, while increasing the urethral closure pressure. At least one of the anticholinergics; Flavoxate, can be used together with alpha-adrenergic and/or oestrogens for treatment of UI. The therapy can be initiated after ruling out cystitis, and we suspect a detrusor instability (Reichler & Hubler, 2014). The detrusor muscle is a part of the urinary bladder wall.

8.5. Surgical management of urinary incontinence

In cases where there is an incomplete response to, or total failure of, medical management, surgery can be helpful in managing UI. In addition, surgery may be useful in case side effects to the medicines develop, or if the owners do not want to medicate their animals long term (Noël et al., 2010b). There is a variety of different methods that can be used, and their goal is to increase the resistance of the bladder neck to the urine flow. The most commonly used surgical procedures are based on either relocation of the bladder neck into an intraabdominal position, increasing the urethral length or increasing the urethral resistance (White, 2016). The first group of surgeries comprises the colosuspension, urethropexy and cystourethropexy. The next groups include bladder reconstruction techniques. Of the incontinent patients submitted for surgery, only a small portion are suitable for these kinds of reconstruction procedures. The last group of surgeries comprise techniques designed to increase urethral resistance by implantation of a prosthetic material or device. Performing surgeries in patients with UI is not common, especially not in Norway. As there are very few patients with this condition in Norway, and most respond well to medicinal therapy, these surgeries are not routinely used in the small animal hospitals.

8.5.1. Colosuspension

Colosuspension is a technique used to relocate the bladder to an intraabdominal position, which can be used to improve UI patients. This is the most often used surgical therapy, and it has a success rate of at least 50%. The technique is performed by anchoring the lateral walls of the vagina to the prepubic tendon. In this way, the bladder is moved into the abdominal pressure zone, cranial to the point of the pelvic brim. In case of a rise in intra-

abdominal pressure, the pressure acts on the bladder and urethra in such a way that any increase in intra-vesical pressure will be counteracted by an equal rise in urethral pressure. This can lead to continence and be helpful for the UI patient (White, 2016). In a case study performed on 150 bitches, it was reported that 56% of the bitches became continent after surgery alone. Further 40% had significant improvements. 10% of the bitches exhibited refractory incontinence based on owner evaluation. Despite these encouraging results, follow-ups have revealed that the percentage of bitches staying continent one year after treatment is only around 14%. The surgery can, however, give much better results when combined with medicinal therapy. It was shown that many of the patients who had undergone surgery had much better results from consequent drug therapies (Noël et al. 2010). Placing the bladder under tension by repositioning the vagina also imposes a risk of failure for this procedure (White, 2016).

8.5.2. Urethropexy

The technique called urethropexy was described in 2001 by White, and was performed on 100 bitches with great results. 56% of the dogs achieved full urinary continence, and a further 27% had improvements to their incontinence. Complications were described among these patients as well, and the most common were dysuria, frequent urination and, in rare cases, complete urinary obstruction. This technique is, similarly to colosuspension, based on a cranial repositioning of the bladder. The method used to achieve this is as follows: the urethra is anchored to the ventral abdominal wall at the level of the cranial point of the pubic brim. Placing two polypropylene sutures ensures that this manoeuvre to be done successfully. The sutures go through one prepubic tendon to the other, through the muscular layers of the urethra, without penetrating into the lumen (Noël et al., 2010b). By positioning the bladder more cranially, any rise of intra-abdominal pressure is allowed to act on both the bladder and urethra. In this way the urethral resistance to urine flow can be increased (White, 2016).

8.5.3. Cystourethropexy

Another surgical method that can be used is cystourethropexy. The aim with this method is, similarly to the previous, to restore the position of the bladder neck and proximal urethra to an intraabdominal position, while increasing the resistance of the urethra to urine flow. With the help of six to ten horizontal mattress sutures, the proximal urethra and bladder neck are anchored to the ventral abdominal wall (Noël et al., 2010b). Together with medicinal

therapy, continence can be restored in some patients. The improvements are, however, temporary in most cases (White, 2016).

8.5.4. Combined colosuspension and urethropexy

It was recently suggested that unless the entire urogenital system was freed after urethropexy and colosuspension, they could not provide persistent results. The urinary and genital components should have to be anchored in a more physiological position. The long-term outcome of combined urethropexy and colosuspension have been reported. The results from the owners showed that more than 90% of the bitches were graded as "excellent" or "good", which is better than the previous results for urethropexy and colosuspension alone. The explanation for these good results are still not clear (White, 2016).

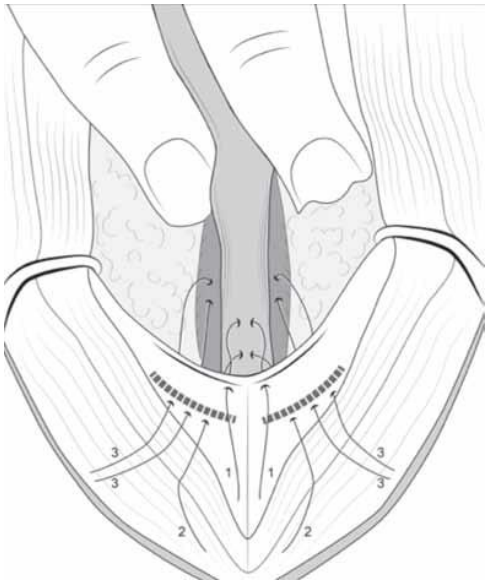

Figure 4: Placement of sutures for the combined colosuspension and urethropexy: 1: linea alba to urethra, 2: prepubic tendon to urethra, 3: prepubic tendon to vagina (White, 2016).

In 1985, Holt stated that no single surgical procedure could resolve all the problems in connection with UI (White, 2016). On the basis of this, we can assume that a combined urethropexy and colosuspension would have improved results, as they improve the continence via different mechanisms of action. In addition to Holt´s statement, a more complete urogenital support seems to result in lower complications and relapses. This supports the hypothesis that a combined method reduces the risk of avulsions of the urethropexy sites. With this information, it is today believed that a combined urethropexy and colosuspension is the first line surgical management of USMI in patients submitted for surgery.

8.5.5. Peri-urethral injections

There are also other therapy methods available, aside from medicinal therapy and surgery. Firstly, we have therapeutic opportunities with endoscopic peri-urethral injections. In these cases, Teflon (polytetrafluoroethylene) or glutaraldehyde cross-linked collagen is injected submucosally via urethroscopy. The result of this therapy is urethral bulging and thereby partially obstructing the urethral lumen, consequentially giving an improved urethral closure pressure. Promising results were recorded, as 68% of the dogs regained full continence. Further 25% had significant improvements following the procedure. Unfortunately, approximately two thirds of the patients have reoccurring urinary incontinence. Results proved to be mainly temporary. Despite the rates of recurring patients, many dogs responded well to repeated therapy (Noël et al., 2010b).

8.5.6. Urethral sling

Urethral sling is a method that also can be used to treat urinary incontinence. The method is either performed using synthetic materials, or flaps from the bladder wall. Urethral sling method can be combined with colosuspension for better results; to further increase mid urethral resistance. It is still unclear whether it is advantageous to use a combination of the two, as it looks to be as effective as if only doing the colosuspension alone (Noël et al., 2010b).

8.5.7. Urethral lengthening

Urethral lengthening is yet another method that can be used for therapy of urinary incontinence. This particular method is used to treat UI secondary to congenital defects in dogs and cats. Urethral lengthening involves procedures to create two full-thickness v-shaped flaps on the ventral aspect of the bladder wall. The defect is closed to decrease the diameter of the bladder neck. Only a few results have been noted, in eight cats the results were excellent. In one dog, it was good (Noël et al., 2010b).

8.5.8. Sphincter reconstruction

In addition, there are sphincter reconstruction techniques, in which a urethral sphincter is created using muscle flaps, or artificial sphincters. So far, these methods have only been described experimentally, and have not been evaluated clinically (Noël et al., 2010b). As urinary incontinence is also of great importance in human medicine, intensive research is ongoing to try to find alternative therapy methods. Especially cell therapy is widely

explored. This includes bone marrow stem cells, adipose cells, amniotic fluid derived stem cells, and autologous skeletal muscle precursor cells is currently proposed for research (Reichler & Hubler, 2014).

8.6. USMI in male dogs

Urinary sphincter mechanism incompetence is also described in male dogs, but it is much less common in the male dog population. USMI represents less than 4% of all incontinent male dogs. It can even be a congenital or acquired condition. USMI is most often seen in adult male dogs. These patients typically have controlled urinations, but experience leakages when there is an increased intra-abdominal pressure. The pathophysiology and treatment in males are not as well understood as in bitches. The diagnosis is made on the basis of history, and ruling out other possible causes for the symptoms. The response rates to medical treatment is significantly poorer, as well. Like in bitches, it is more common for USMI to occur in larger breed dogs, and it has been shown that castration can predispose to the condition (Verde & Crivellenti, 2012).

9. Practical examples

I have collected two patient anamneses from the clinic in Norway where I had my small animal practice, in addition to one from another student. These three bitches have become incontinent after spaying. Two have been treated with Incurin (oestriol), and one with Propalin syrup (Phenylpropanolamine HCl). As spaying is not performed routinely in Norway, it was not easy to find a high number of patients. At the clinic where I had my practice, I only found these two patients with the diagnosis USMI after spaying. I made a questionnaire regarding the success of the therapy and called the owners to see how the therapy was going. The patients are described with signalment and anamnesis. The responsible veterinarians have chosen different drugs for therapy based on own experiences and what they are used to in the clinic. These patients are not representative for the entire population of incontinent spayed bitches, but they provide a closer look into how successful the therapy have been for the given patients, and therefore gives an idea of the success of our most used medicines. The owners and veterinarians have agreed to using the patient data for my thesis.

9.1. Patient #1

Signalment:

Gender and species: Female dog.

Breed: Eurasier (Large breed dog).

Age: 10 years old (Born April 2006).

Anamnesis:

In 2009, at the age of 3 years, the bitch became sick and was diagnosed with pyometra. As a result of this, she was immediately spayed. In 2010, 1 year after the spaying, she was brought to the clinic for a routine vaccination. At the same time, the owners could tell the veterinarian that she had been dribbling urine for the last 3-4 weeks. Otherwise, the dog was in a good health condition. The owners wondered if this urine dribbling could be a side effect from the spaying.

Clinical examination:

The clinical examination was good, with no deviations from the normal. The veterinarian performed a urinalysis from the urine. The results from the urinalysis were: pH = 6.5, pro TR, UBG 1 mg/dl, S.G. = 1.038, LEU GLU KET neg. Microscopy of the urine sediment turned out negative.

Diagnosis:

Urinary incontinence after ovariohysterectomy.

Therapy:

Incurin tablets (Oestriol) 1 mg. The instructions regarding the dosage was to start with 1 tablet per day, thereafter ½ tablet until the desired effect had been reached, and after this ½ tablet every second day.

I called the owner to ask how the therapy is going, and asked her some questions:

1) After starting the Incurin treatment, how long time did it take for the incontinence symptoms to disappear?
   It only took a few days; we saw a very rapid improvement.
2) Has she been stably free from symptoms since the start of medicinal therapy?
   Since the beginning of medicinal therapy, she has been free from symptoms every day. The owners are absolutely satisfied with the results of the therapy.
3) Have you observed any side effects from the medicinal therapy?
   No.
4) What dosage are you giving?
   ½ tablet of Incurin every day.

9.2. Patient #2

Signalment:

Gender and species: Female dog.

Breed: Medium Poodle (Large breed dog).

Age: 10 years old (Born April 2006).

Anamnesis:

This patient was spayed at age of three years old, as she had been suffering from deep chronic pyoderma in connection with estrus every time she came into heat. Her estrous cycle was irregular, and her skin problems blossomed at the time of estrus. The veterinarian had tried to solve her hormone-induced dermatitis with conservative therapy, but it was not successful. The only chance for recovery seemed to be OHE, and she was therefore spayed. In 2010, one year after spaying, the dog came to the clinic with incontinence symptoms.

Clinical examination:

The clinical examination was negative, the veterinarian found no abnormalities. Urinalysis: negative, without remarks.

Diagnosis:

Urinary Incontinence after OHE.

Therapy:

Incurin (1mg) tablets. 1 tablet daily.

I called the owner to ask how the therapy is going, and asked her some questions:

1) After starting the Incurin treatment, how long time did it take for the incontinence symptoms to disappear?
   It only took a few days; we saw a very rapid improvement within 1 week.
2) Has she been stably free from symptoms since the start of medicinal therapy?
   No. The dog lives together with the dad most of the time, but some days she lives with the mother. At the dad´s house, she is free from symptoms, and only has approximately 1 accident every 3-4 months. At the mother´s house, she is generally stressed and has accidents inside the house every day. These are believed to be due to behavioural problems and stress.
3) Have you observed any side effects from the medicinal therapy?
   No.
4) What dosage are you giving?
   ½ - 1 tablet of Incurin every day. It depends on if she is at the dad´s or mother´s place. If she is at the dad´s house; ½ tablet is enough. If she is at the mother´s house, they have to give her 1 tablet for improved effect.

9.3. Patient #3

Signalment:

Gender and species: Female dog.

Breed: English Greyhound (weight: 22 kg. Large breed dog)

Age: 6 years (Born November 2010)

Anamnesis:

This dog was spayed at the age of 1 year in Budapest as she was going to be adopted. Almost three years after the spay (October 2015), she started showing typical symptoms of urinary incontinence. She was therefore brought to the veterinary clinic for a clinical examination.

Clinical examination:

Blood haematology and biochemistry were negative, without significant remarks. Urinalysis was negative.

Diagnosis:

Urinary Incontinence after OHE.

Therapy:

Propalin syrup (Phenylpropanolamine HCl).

I asked the dog's owner some questions regarding her therapy:

1) After starting the Propalin syrup treatment, how long time did it take for the incontinence symptoms to disappear?
   The symptoms ceased after a few days of starting medical therapy, and urine leakage ended within a few days.
2) Has she been stably free from symptoms since the start of medicinal therapy?
   Yes.
3) Have you observed any side effects from the medicinal therapy?
   No.
4) What dosage are you giving?
   We started with 0.5 ml q12 h daily. When the symptoms were gone we started to gradually decrease the dosage, and found an appropriate dosage to be 0.4 ml q12 h daily PO with food. Today, the dog is even doing well off her medications. She has moved to Norway, and seems more relaxed, and therefore the owner is trying to not give her medicines for a time period.

9.4. Case summary

These three cases are not sufficient to draw any conclusions in regards to the success of the UI therapy broadly speaking. They can, however, be representative for the typical patient group at a small animal hospital in Norway. There are not many affected bitches due to the spay routines in the country. All three cases have a successful outcome of the therapy, as the patients have improved in all the cases. Even though two of them are on Oestriol therapy, and one is on PPA, none of the patients have experienced side effects of the therapy.

One of the bitches; Patient # 2, is still experiencing incontinence on various levels. These accidents are believed to be due to environment changes. According to the owner, the dog is relaxed when she lives with the dad, and stressed when she lives with the mother. Accordingly, she has accidents every day when she is with the mother, and almost never when she is with the father. Therefore, they increase the Oestriol dosage when she is with

the mother, to try to help avoid the incontinence. Although she is not completely continent after starting with the drug therapy, the owners could explain that they saw a rapid decrease in accidents soon after starting the therapy. We can therefore understand that she had an improvement due to the medications, and that she has behavioural problems complicating her case. Today she is much better due to her medications, and the family is therefore somewhat happy with the outcome of the medications.

Patient # 1 and Patient # 2 started showing incontinence symptoms around one year after the spaying. Patient # 3 started showing symptoms around three years after her surgery. All of these are within the "normal" range of timing of incontinence. However, the mean average between 2-5 years (Reichler & Hubler, 2014), is only true for one of these patients. This proves that all cases are unique, and the symptoms may start at various time points after the surgery.

These three patients also fit well into the "classical" incontinence profile, as they are large sized, with a body weight over 20 kg. The general rule is that the higher the body weight, the higher is the risk of developing UI (Reichler & Hubler, 2014). The patients are not representative to conclude to anything, but they point to the fact that more often the larger sized breeds are affected by USMI than the smaller breeds. Another factor, which characterized all three patients, is that they all experienced a rapid improvement after starting the medicinal therapy. The owners of the dogs all reported that the incontinence symptoms disappeared within a few days, and that they became continent within a week. This can tell us that the medicinal therapy is successful in most cases.

10. Summary

The exact reason and pathogenesis for development of UI in spayed bitches is not yet completely understood. We can understand several of the different changes in the body caused by the gonadectomy, and what affect they might have on the organ systems. However, we cannot say exactly why USMI develops in some bitches, and not in others. The risk of developing UI after spaying is relatively high (up to 20%) and should be considered and informed about when making the decision to spay the bitch. Considering previous studies and information, we cannot eliminate or significantly lower this risk by performing the surgery at an early age.

There are good therapy options in regards to treating UI in spayed bitches. The first drug of choice is PPA. This medicine has very good results, and a high success rate. However, it is not optimal for all patients, and may not be helpful in every single case. Luckily, we have other options like Oestriol and GnRH-analogues. Additionally, surgery is a possibility to help incontinent patients. Medicinal therapy seems to be effective and very often successful. Even though I have not looked in to a representative number of cases to draw any conclusions based on this, I have received information from some owners in regards to the success of the medications. This leads me to believe that UI is a condition that in most cases can be easily managed with the help of medicinal therapy. In cases where this does not work, we can also try surgical options.

In regards to establishing a diagnosis of an incontinent bitch after spaying, it is important that the veterinarian make a proper anamnesis and clinical examinations. By eliminating other causes like congenital malformations and UTI´s, we can easily establish a diagnosis. Blood haematology, biochemistry and urinalysis is helpful in making the diagnosis. The anamnesis is important as most of our incontinent patients show typical symptoms and patterns when presented to our clinic. Even though we cannot draw a conclusion based on symptoms, they are very helpful in pointing us in the direction of the diagnosis.

More studies in this area would be helpful in understanding better how the urinary incontinence develops, and how we might be able to lower the risks of development in the future. This is a potential area of great interests, and there are aspects of the pathogenesis we need study more to be able to understand USMI to a better degree.

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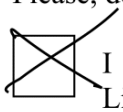

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