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TWO COMMON CAUSES OF INFERTILITY IN THE MALE DOG

Prof. Stefano Romagnoli, DVM, MS, PhD

Diplomate European College of Animal Reproduction
Department of Veterinary Clinical Sciences
University of Padova Agripolis
Legnaro 35020 (PD)
Italy
stefano.romagnoli@unipd.it

1. BENIGN PROSTATIC HYPERTROPHY

Benign prostatic hyperplasia (BPH) is the most common canine prostatic disorder, with almost 100% of intact dogs developing histologic evidence of BPH with aging. BPH is characterized by an increase in epithelial cell numbers (hyperplasia) as well as an increase in epithelial cell size (hypertrophy), but the increase in cell number is more marked. It begins as glandular hyperplasia in dogs as young as 2.5 years of age. Intraparenchymal fluid cysts may develop in association with hyperplasia. Such cysts are variable in size and contour, contain a thin, clear to amber fluid and, if intraprenchymal, may communicate with the urethra thus leading to intermittent haemorrhagic or clear, light yellow urethral discharge.

Etiology: Hyperplasia is probably due to an altered androgen: estrogen ratio, and requires the presence of the testes to start and continue to develop. Dihydrotestosterone (DHT) within the prostate gland probably serves as the main hormonal mediator for hyperplasia. The hyperplastic prostate is highly vascularized and therefore the gland bleeds easily, which explains the common clinical sign of blood from the tip of the penis or blood in the urine. Blood loss in the prostatic urethra can be so intense that the ejaculate may appear completely red. Although presence of blood in the semen is typically considered to be a cause for infertility, dogs with some blood in their ejaculates may sometimes be fertile. The reason for BPH being a common cause of infertility in the dog is probably due to the alteration of the biochemistry of the prostatic fluid whose important action of nutrition of spermatozoa is decreased. Prostatitis or abscessation are likely consequences of presence of blood in the prostate.

Diagnosis: An enlarged, hypertrophic prostate may cause blood dripping from the tip of penis, or it may grow and expand in the rectal canal, causing tenesmus and sometimes difficult defecation. Other than the above signs, affected dogs are usually normal and the prostate on palpation is non-painful, symmetrically enlarged and with variable consistency. Urine may contain blood (gross or microscopic). If hyperplasia is accompanied by urethral discharge, this is typically haemorrhagic or clear but not purulent. Prostatic enlargement may be visualized on abdominal radiography as causing dorsal displacement of the colon and cranial displacement of the bladder. On retrograde urethrocystography the prostatic urethra may be normal or narrowed and undulant with mucosal irregularity, and the urethroprostatic reflux may be normal or greater than normal. On ultrasound, the prostate may appear diffusely hyperechoic with parenchymal cavities (which means that intraprenchymal cysts have developed). The canine prostate is best evaluated in the sagittal and transverse planes using 5.0 or preferably 7.5 MHz scanners. An enema should be administered prior to scanning to eliminate colonic contents which may mimic peripheral prostatic disease. Conditions such as cysts or abscesses are visualized easily. Other less distinct but echogenically complex areas may indicate neoplasia or areas of infection within the gland. Although technically a definitive diagnosis of BPH is only possible by biopsy, such an invasive approach is not necessary to institute a therapy if clinical signs are present, and from a practical standpoint ultrasound assessment of prostatic size and presence of cysts is often the only thing that is necessary to identify the problem and start dealing with it. No alteration of haematological or biochemical parameters are commonly observed in dogs with BPH.

Treatment: If the dog is asymptomatic owners should be advised to watch for the development of clinical signs in order to start treatment as soon as possible. The most effective treatment is castration, following which prostatic size may decrease as much as 50% in 3 weeks and 70% over 9 weeks. As post-castration involution begins within days of surgery, clinicians should palpate the dog's prostate 3 weeks post-operatively

to make sure the involution rate is normal thus ruling out a more serious prostatic disease such as neoplasia or abscessation. When castration cannot be considered, drugs such as estrogens, steroidal or non-steroidal antiandrogens or GnRH agonists can be used. Estrogens act indirectly by reducing androgen concentrations through an inhibition of gonadotropin secretion/release by the pituitary. Prostatic size is thus decreased through a reduction of cellular mass. Size and number of intraparenchymal cysts may not be affected. Because of the potential risk of serious bone marrow side effects (anemia, leukopenia, thrombocytopenia, pancitopenia) as well as because of the risk of growth of the fibromuscular stroma of the prostate, metaplasia of the prostatic glandular epithelium and secretory stasis resulting in prostatic enlargement and predisposition to cyst formation, bacterial infection and abscessation, the clinical use of estrogens to treat prostatic hyperplasia is currently not advised.

Steroidal Antiandrogens: Steroidal antiandrogens compete with androgen receptors and perhaps also with DHT receptors at the cellular level in target organs. Compounds such as megestrol acetate, medroxyprogesterone acetate, delmadinone acetate, chlormadinone acetate and ciproterone acetate are successfully used in the dog, although for the majority of them there is only a limited amount of experimental data on their effectiveness in the dog. Their action causes a sort of pharmacologic castration and is rather precociously observed during treatment, as improvement can be observed already after 7-15 days. Megestrol acetate can be used at the dose of 2.2 mg/kg per os MID for a maximum of 2 weeks, or at the dose of 0.55 mg/kg/day PO for 4 weeks. Medroxyprogesterone acetate can be used at the dose of 3-4 mg/kg SC every 10 weeks. Chlormadinone acetate can be used at the dose of 1-2 mg/kg orally for 1 month, or as a subcutaneous implant of 5.0 mg/kg which lasts for 12 months. Recent studies done at the University of Pisa, Italy, show a good clinical effect on cases of dogs suffering from prostatic disease when treated with ciproterone acetate at the daily dose of 0.5 mg/kg per os. All steroidal antiandrogens should not be used in breeding animals as their prolonged use will remarkably decrease libido and fertility.

Non-Steroidal Antiandrogens – Non-steroidal antiandrogens include finasteride and flutamide. Finasteride inhibits 5-a-reductase (the enzyme responsible for the final transformation of testosterone into di-hydro-testosterone or DHT) thereby lowering the concentration of DHT which is the active metabolite at the level of target tissues, without altering serum testosterone concentrations. This leaves spermatozoa production undisturbed, which makes finateride a good choice for breeders (although a chronic use may be associated with a decrease in ejaculate volume as well as decrase in semen quality). Finasteride is only approved for use in men, but it is well known to produce a dose-dependent decrease in prostatic size also in dogs. It can be used at the daily dose of 1.5 mg (approximately 1/3 of a 5.0 mg pill) for dogs ≤15 kg body weight, 2.5 mg (approximately half pill) for dogs of 15-30 kg body weight, and 5.0 mg for dogs of >30 kg body weight. Finasteride is well tolerated and can be administered for long periods of time. However, as soon as it is discontinued the prostate will start growing again. Flutamide is a human antiandrogen which can cause a significant decrease in prostatic size as detected by ultrasonography within 10 days. When administered to research dogs at 5 mg/kg/day PO for 1 year, it did not alter libido or sperm production. In most countries flutamide is not approved for use in veterinary medicine, although it appears safe, effective and well tolerated in dogs.

GnRH Agonists: A recent development in the field of control of prostatic disease in dogs is the use of agonists of GnRH disolved in a lipid base. GnRH agonists act by down-regulating GnRH receptors at the gonadotropes in the pituitary, thereby suppressing the function of the hypothalamic-pituitary-gonadal (HPG) axis. Their suppressing action, generally devoid of side effects, is the result of a continuous release provided by the delivery system. Suppression of the HPG axis leads to suppression of release of LH and FSH with consequent lack of secretion of estrogens, progesterone and testosterone as well as their by-products. Such blockade of steroidogenesis can be used in small animals for a variety of indications including the reduction of prostatic size thereby helping in the control of BPH. In experiments performed in the dog, prostatic size decreases in parallel with the decrease of testosterone following administration of a GnRH agonist. When adult dogs are implanted with deslorelin at a dose of 0.5-1.0 mg/kg body weight, their prostatic volume decreases more than 50% and serum testosterone concentrations decreases 90% already from the 6th week of treatment when compared to controls. Once treatment is discontinued, prostate returns to approximate pre-implantation volume by week 48. Therefore, use of GnRH agonists can effectively help in the treatment of prostatic disease such as benign prostatic hyperplasia.

2. AZOOSPERMIA

Azoospermia means ejaculation of seminal fluid devoid of spermatozoa. Its incidence in the dog is estimated to be around 35%. Dogs may fail

to ejaculate the second, sperm-rich fraction if they feel uneasy or apprehensive at the time of semen collection and/or if there is no bitch in heat present. In such cases only the pre-sperm fraction is ejaculated, which is prostatic fluid. Some dogs need to be trained to give semen through manual stimulation, and this may require repeating the procedure a few times in the presence of a bitch in full heat. Before a diagnosis of azoospermia is confirmed, semen collection should be repeated (in a trained dog) at least 3-4 times over several days. Whenever an azoospermic sample is collected, carnitine or alkaline phosphatase (AP) should be measured on seminal plasma. Both compounds are secreted in the epididymis and their concentration is high in normal semen. While carnitine assay is not often easy to achieve, AP can be measured using normal clinical chemistry laboratory equipment. Normal dogs with semen coming from the testicles have AP values > 5.000, while when an incomplete sample is collected AP is < 5000 U/L but often even < 2000 U/L. Therefore, assaying AP is a good way to distinguish on the source of the collected sample. Seminal plasma AP is measured by laboratory equipment routinely used to measure the enzyme in serum. Seminal plasma samples must diluted properly as AP concentrations is normally very high (> 5.000 U/L, but often > 20.000 U/L) and therefore gets out of the normal range for a reference serum AP assay. Laboratory technicians should be advised to centrifuge the semen sample (some sophisticated equipments may be damaged by spermatozoa) and also to dilute the centrifuged sample as seminal plasma AP concentrations may be as high as 40.000 IU/L, and the result of the undiluted sample could be so high that might be not readable. An azoospermic semen sample with high AP comes from the testicles, while an azoospermic sample with low AP may come from the prostate (indicating incomplete ejaculation) or its source is however posterior to the epididymis (indicating bilateral duct outflow blockage. When AP concentrations are equivocal, two ejaculates may be collected 1 hour apart and AP can be assayed on the second one, which gives a higher accuracy.

Azoospermia is more commonly diagnosed in purebred adult (3-7 years of age) dogs, although it may also occur in crossbreds. Azoospermic dogs may have sired one or more litters previously. In the few reports in the literature about this condition in the dog, the Labrador breed seem to be at a somewhat higher risk than other breeds. Heritability is suspected as azoospermic related Scottish terriers and Labrador retrievers have been reported, with 2 male offsprings of an azoospermic Labrador retriever becoming infertile between 2 and 7 years of age (while another male offspring was fertile until the age of 12).

Etiology: Azoospermia may be due to pre-testicular, testicular or post-testicular factors. Pre-testicular factors include endocrine conditions such as hypopituitarism, hypothyroidism, steroid excess (Cushing syndrome or exogenous steroid administration), or treatment with antineoplastic drugs, inguinal or scrotal hernia. Prolonged fever may also cause spermatogenic dysfunction, although in humans fever is responsible for a decline in semen quality but not for azoospermia. Testicular causes of azoospermia include intersex, germinal cell aplasia, bilateral cryptorchidism, testicular injury due to trauma, irradiation, thermal insult, orchitis, autoimmune testicular disorders (such as spermatogenic arrest) and testicular cancer.

The following intersex condition may cause azoospermia: **female pseudohermaphroditism** refers to individuals with male external genitalia and female gonads, is rather uncommon and is due to masculinization of female fetuses in utero due to exogenous hormonal treatment of the dam in pregnancy; 79,XXY characterized by hypoplastic testicles, lack of spermatogenesis and underdeveloped external genitalia; presence of spermatozoa in the ejaculate of affected dogs is poorly reported, but is thought to be rare as only 6% of humans with this conditions can be fertile; **XX sex reversal** characterized by presence of male external genitalia and testicular and/or ovarian gonadal tissue in a dog with a 78,XX karyotype, has been reported in Kerry blue terriers, pugs, English cocker spaniels, Beagles, Weimaraners and German shorthaired pointers; affected dogs are sterile.

Germinal cell aplasia occurs in about 10% of azoospermic dog and is characterized by presence of only Sertoli cells. From the histologic point of view germinal cell aplasia may be not distinguishable from testicular atrophy unless fibrotic changes are also present. Bilateral cryptorchidism causes degeneration of the germinal cell line without altering Sertoli and Leydig cell function, which means that endocrine function is normal in these dogs. Orchitis and/or epididymitis may determine fibrotic changes of the duct system causing stenosis which results in oligozoospermia and frequently evolves in azoospermia despite antibiotic treatment. Autoimmune orchitis has also been associated with azoospermia. Autoimmune orchitis in the Beagle is reported to occur concomitantly with autoimmune thyroiditis, as evidenced by a rise in the concentration of serum thyroid autoantibodies in these azoospermic individuals. Sertoli cell tumor may cause azoospermia either by direct

destruction of testicular tissue, inflammation, rise in intratesticular temperature and/or altered estrogen:androgen ratio exerting a negative feedback on the hypothalamic-pituitary axis.

Post-testicular diseases responsible for azoospermia are those which cause outflow obstruction such as spermatocele, sperm granuloma or segmental aplasia of the epididymis. Incidence of post-testicular causes of azoospermia in humans is ≤1% while it is unknown in dogs.

Diagnosis: No specific clinical signs has been associated with azoospermia in dogs: although often smaller and softer than usual, testicles of affected dogs may be normal in size and consistency. Testicular degeneration and softening of both testicles is reported in dogs after bilateral vasectomy or bilateral ligation of the cauda epididymis, which seems to suggest that an altered consistency of testicular tissue may occur in dogs with an outflow obstruction (obstructive azoospermia). Libido is usually normal to excellent in affected dogs.

Diagnosis of azoospermia needs to be confirmed by repeating semen collection, and characterized by localization and type of defect present. Measurement of AP is of utmost importance in confirming and characterizing the diagnosis, its concentration being low in male dogs with bilateral outflow obstruction. Epididymal abnormalities may or may not be palpable or even visible ultrasonographically. Fine needle aspiration of the cauda epididymis may help rule out absence of spermatogenesis but does not differentiate between outflow obstruction and incomplete ejaculation; since extravasation of spermatozoa may lead to development of sperm granulomas, less invasive techniques should be considered in the initial diagnostic process. If an azoospermic semen sample has high AP concentration, pre-testicular and testicular causes should be carefully investigated. The clinical approach includes a complete physical examination, endocrine testing (thyroid hormone testing ACTH measurement and ACTH stimulation or dexamethasone suppression test, as well as measurement of FSH and LH), karyotype, culture of ejaculated seminal fluid for aerobic and anaerobic bacteria and mycoplasma cytology of the sediment of the seminal fluid following centrifugation, testicular/epididymal ultrasonography, and Brucella canis serology.

Serum LH and FSH are normal to slightly elevated in dogs with gonadal failure. FSH concentrations increase in dogs with testicular disease and its rise correlates with degree of severity of spermatogenetic alteration. As spermatogenesis progressively decreases, testicles produce less and less inhibin which results in higher and higher concentration of FSH being released from the pituitary. Both FSH and LH are released in pulses from the pituitary, therefore their assay requires frequent blood samplings (3 samples at 20-minute intervals) or a GnRH stimulation test using 50-100 mcg of GnRH IV and collection of a basal (pre-GnRH) sample followed by a second sample collected after one hour. Normal LH, FSH and testosterone concentration in the adult dog post GnRH stimulation are approximately 30 ng/ml, 60-300 ng/ml and 1-4 ng/ml, respectively.

Karyotype (normal male dogs have 78,XY) should be performed in all dogs with a congenital problem, e.g. those dogs who have never sired a litter and/or with abnormal or immature external genitalia. Definitive diagnosis of azoospermia requires assessment of testicular function by aspiration or biopsy of a tsticular specimen. Fine needle aspirate is a good technique for confirming presence of an outflow obstruction and ruling out germinal cell aplasia, but in case of soft testes it generally does not deliver enough cells to make a diagnosis. Although more invasive techniques will yield more adequate samples, cost, risk for the animal (including anesthesia) and value of the data obtained for treatment generally do not justify using a core or incisional biopsy for an azoospermic dog, especially if testicular volume and consistency are greatly decreased. Testicular histology in azoospermic dogs is highly variable, with many dogs showing some evidence of normal spermatogenesis (≥50% of normal seminiferous tubules). The fact that a certain percentage of testicular parenchima appears to be normal is not necessarily of good prognostic value. When a bilateral outflow obstruction is diagnosed, often this is a result of a chronic inflammatory disease causing stenosis of the duct system at various levels. In humans, bilateral outflow obstruction is treated with 5-15 mg prednisone/day orally (based on body weight) for one month, after which semen collection is attempted; such treatment is often successful although ductal patency is not permanently restored and outflow obstruction frequently recurs after some time.

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