

Common causes of male dog infertility

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Abstract

A complete breeding soundness evaluation is essential for assessment of the infertile male dog. Cryptorchidism, a sex-limited autosomal recessive trait, is more common as a unilateral condition. Azoospermia is an ejaculate consisting of seminal plasma but lacking sperm; repeated semen collections in the presence of an estrual bitch will rule out inadequate experience and lack of sexual stimulation. Both carnitine and alkaline phosphatase (AP) are produced in the epididymis; seminal plasma AP concentrations >5000 U/L indicate a normal ejaculate, whereas <5000 U/L is associated with incomplete ejaculation. Benign prostatic hypertrophy (BPH), the most common age-related condition in intact male dogs, is characterized by a sanguineous urethral discharge, hematuria, or hemospermia; diagnosis is based on prostatic enlargement and confirmed by a transabdominal biopsy. Although castration is recommended, valuable breeding dogs can be given finasteride. Prostatitis is more common in older dogs with BPH. Culture of the third fraction of the ejaculate or urine obtained by cystocentesis is indicated. Bacterial prostatitis is treated with antibiotics with high lipid solubility. Some dogs with bacterial prostatitis may develop prostatic abscesses (a medical and surgical emergency). Prostatic cysts are often asymptomatic. Approximately, 5–7% of dogs with prostatic disease have prostatic neoplasia, most commonly adenocarcinoma (it occurs in both intact and castrated dogs), which often metastasizes and has a very poor prognosis. Although a specific diagnosis can be made in many cases of male dog infertility, not all causes are amenable to treatment.

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1. Introduction

Dog infertility results in substantial financial losses to the ever-expanding canine breeding industry. This paper will briefly review current information regarding common causes of male dog infertility, diagnostic methods, and treatment.

History, including general health and reproductive performance, followed by thorough physical examination, are key initial steps in the assessment of an infertile male dog. Conditions involving the prostate gland or

testicular dysfunction require a comprehensive breeding soundness evaluation (BSE), including collection and evaluation of semen, palpation and measurement of testes, digital palpation of prostate, and potentially ultrasonography of the testes and the prostate. Breeding dogs are tested for brucellosis. Depending upon the initial diagnostic results, dogs may require endocrine testing (e.g. reproductive or thyroid hormones), karyotyping, semen culture, and testicular biopsy.

The history should include overall health, vaccination status, nutrition, management, and housing. Reproductive history includes breeding outcomes (if the dog has been used for breeding): breeding management of the bitch (vaginal cytology, serum progesterone analysis), AI with chilled transported

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semen, frozen-thawed semen, pregnancy detection techniques used (e.g. ultrasonography, radiography), number and sizes of litters, and fetal viability.

2. Cryptorchidism

Information regarding cryptorchidism is adopted from the author's earlier review on the topic [1]. There should be two normal testes present in the scrotum of a breeding dog. The term cryptorchid means hidden testis; a non-castrated male with no testes present in the scrotum is a bilateral cryptorchid, whereas a male with only one testis in the scrotum is a unilateral cryptorchid. Unilateral cryptorchidism occurs more commonly than the bilateral condition. Owners of cryptorchid dogs often inquire "How long can I wait before concluding that the undescended testis is not going to come down?" Testicular descent is complete by approximately 10 days after birth in normal dogs [2]. Some owners of cryptorchid animals may report the presence and subsequent disappearance of scrotal testes. In a newborn puppy, the testes are small, soft and can move between scrotum and inguinal canal, especially when the pup is stressed or frightened [3,4]. It is recommended to wait up to about 6 months of age before declaring a dog cryptorchid; the inguinal rings of most dogs are closed by 6 months of age, precluding movement of the testes from the abdomen to the inguinal canal if that has not already occurred [5].

Cryptorchidism is heritable; it is a sex-limited autosomal recessive trait in dogs [5]. The incidence of cryptorchidism seems to be higher in purebred and inbred dogs than in mixed-breed dogs. A high prevalence of cryptorchidism within lines of inbred Cocker Spaniels and miniature Schnauzers has been reported [6,7]. Cryptorchid dogs have increased frequencies of other congenital defects, including inguinal and umbilical hernias, patellar luxation, and preputial and penile problems. Retained testes are predisposed to neoplasia (9–14 times higher than in the scrotal testis [8,9]), with sertoli cell tumors and seminomas being the most common tumors [10]. In addition, torsion of the spermatic cord may occasionally occur with an abdominal testis, leading to peracute abdominal pain and other complications.

A unilaterally cryptorchid animal can produce viable sperm, whereas a bilateral cryptorchid male is usually sterile. Testes should be scrotal (4–5 °C cooler than body temperature) to produce normal sperm. Even though unilateral cryptorchids have reduced semen quality (due to the adverse effect of high body temperature on the retained testis) they can often

impregnate an estrual female. Cryptorchidism however, does not affect testosterone production [11,12]. Therefore, most cryptorchids have libido and can achieve erection [13]. Retained testes are smaller; the diameter of the seminiferous tubules is reduced by up to 60% compared to those of scrotal testes [14].

The incidence of cryptorchidism is higher in small-breed compared to large-breed dogs [15]. Reported incidences in dogs range from 1.2 to 10% [16–18]. The 10 breeds with the highest incidence of cryptorchidism are Toy Poodles, Pomeranian, Yorkshire terrier, Miniature Dachshund, Cairn terrier, Chihuahua, Maltese, Boxer, Pekingese, and English bulldog [5].

2.1. Diagnosis

Visual examination and careful digital palpation of the scrotum and inguinal area are indicated. However, scrotal fat and inguinal lymph nodes may be confused with the retained testis. Abdominal testes are difficult to palpate or detect with ultrasonography. A stimulation test, using either hCG or GnRH to elicit an increase in blood testosterone concentrations, is recommended. The standard protocol is to determine testosterone concentrations in blood samples drawn before and 60 min after im injection of GnRH (2 µg/kg or 50 µg/dog [19]); a substantial increase in testosterone concentrations in the post-treatment blood sample is diagnostic of cryptorchidism.

2.2. Treatment

As discussed above, cryptorchidism is considered hereditary; a dog with this condition should not be used for breeding. Control of cryptorchidism can be best accomplished by removal of affected dogs (and preferably their dam and sires) from breeding programs [20].

Bilateral castration is the treatment of choice. The surgical approach to find and remove the cryptorchid testis is dependent on its location. Although standard surgical techniques are most commonly used, the retained testis may be removed by laparoscopy [21]. The key to finding the retained testis is to identify the ductus deferens and follow it back to the testis.

Orchiopexy (surgically anchoring the retained testis in the scrotum) has been reported. Kawakami et al. [14] reported gradual improvement in semen quality after orchiopexy; 3 of 11 bitches bred were diagnosed pregnant. However, cryptorchid dogs cannot be shown in American Kennel Club shows and treatment by orchiopexy may be considered fraudulent [5]. The most

common medical treatment (excluding acupuncture and herbal preparations), is the hormone treatment (hCG or GnRH) to increase endogenous or exogenous LH activity. However, most studies reporting the success of the hormonal treatment are anecdotal and lack appropriate controls.

3. Azoospermia

Azoospermia is an ejaculate devoid of spermatozoa; only seminal plasma is collected. The incidence of azoospermia is estimated to be as high as 35% [22]. Some dogs do not ejaculate the sperm rich fraction because they are anxious or lack adequate sexual stimulation, especially in absence of an estrual bitch. In these cases, only pre-sperm prostatic fluid is collected. To confirm azoospermia, the dog should be collected in the presence of an estrual bitch. Some inexperienced dogs may require multiple semen collections (with a few days between successive collections) in the presence of an estrual bitch to ensure that azoospermia is not due to inadequate experience or sexual excitement.

Azoospermia is reported in purebred and in crossbred dogs. In the author's experience, some azoospermic dogs had already sired more than one litter. Heritability is suspected, especially in Labrador retrievers and Scottish terriers.

3.1. Etiology

To elucidate the cause of azoospermia, one should consider that the origin of the abnormality is pre-testicular, testicular, or post-testicular. Pre-testicular causes include generalized endocrine disturbances (e.g. hypothyroidism, Cushing's syndrome). Increased testicular temperature, due to scrotal hernia or prolonged fever, may cause testicular degeneration and azoospermia; other potential causes include bilateral cryptorchidism, intersexes, testicular hypoplasia and injury (trauma, orchitis), and testicular neoplasia. Post-testicular causes for azoospermia are primarily conditions causing obstruction to sperm release during ejaculation, including sperm granuloma, segmental aplasia of the epididymis, and spermatocele.

To diagnose azoospermia, it is essential to confirm that the ejaculate was complete and not due to inadequate sexual stimulation. As noted earlier, repeated semen collections in presence of an estrual bitch may be needed to rule out inexperience and inadequate sexual stimulation.

Carnitine or alkaline phosphatase (AP) concentrations of the azoospermic ejaculate should be measured;

both compounds are of epididymal origin. In normal ejaculates, AP concentrations are >5000 U/L [23]; in cases of incomplete ejaculation, it is <5000 U/L and often <2000 U/L. Seminal plasma samples should be diluted prior to analysis, as AP concentrations can be very high (>20,000 U/L) and off-scale for many assays intended for blood serum AP. If the ejaculate contains sperm, it should be centrifuged and only seminal plasma tested (sperm may damage laboratory equipment designed to test serum samples). An azoospermic ejaculate with very low AP represents prostate fluid and may be due to incomplete ejaculation or bilateral duct blockage. To increase accuracy, two ejaculates should be collected (1 h apart) and the AP concentration determined on the second ejaculate [22].

4. Prostate disorders

4.1. Benign prostatic hypertrophy (BPH)

The prostate is a walnut-shaped gland, located caudal to the urinary bladder. It is comprised of two lobes, enclosed by an outer layer of tissue and surrounds the urethra. It produces seminal plasma; during ejaculation, the seminal plasma is secreted into the urethra to dilute the sperm. In prostatic epithelial cells, testosterone, produced by the Leydig cells of the testes, is converted (by 5- α reductase) to dihydrotestosterone (DHT), a much more active form of this hormone that regulates prostatic development and function [24].

Benign prostatic hypertrophy (BPH) is the most common age-related condition in sexually intact male dogs; it was noteworthy that >80% of sexually intact male dogs >5 years of age had gross or microscopic evidence of BPH [25]. This condition is characterized by an increase in epithelial cell numbers (hyperplasia) and in epithelial cell size (hypertrophy). Prostatic volume in dogs with BPH was 2–6.5 times that of unaffected dogs of similar body weight. Prostate size can be measured accurately by ultrasonography; normal dimensions of the prostate in intact dogs have been published [26]. Although the pathogenesis of BPH is not completely understood, DHT is well accepted as a key hormone in men and dogs, stimulating enlargement of the prostate by enhancing growth in the stromal and glandular compartments. There is no known breed predisposition for BPH.

Clinical signs of BPH in men include impaired bladder emptying, difficulty urinating, and hematuria, whereas clinical signs in dogs include constipation, sanguineous fluid dripping from the urethra, hematuria and hemospermia. In one report, 20 of 28 dogs (71.5%)

with BPH presented with sanguineous urethral discharge as the sole clinical sign. Hematuria may be grossly apparent or only detected on urinalysis.

Diagnosis is based on confirmation of prostatic enlargement and exclusion of other prostatic gland disorders (e.g., prostatitis, neoplasia). Aerobic and anaerobic cultures from urine and semen are normal unless infection is superimposed on BPH. Complete blood counts and bacterial cultures from urine are normal. Hemospermia is a common finding in semen collected by manual ejaculation. If a semen sample cannot be collected, a prostatic wash or urethral brush technique may be used to collect prostate fluid or cells [5]. In the brush technique, a sterile microbiologic specimen collection brush within a double-sheathed catheter is passed through the urethra to the level of the prostate. The prostate is vigorously massaged (finger placed in the rectum) for 1 min, and the specimen brush is then advanced and retracted five or six times and withdrawn. The brush and any fluid collected are placed in sterile saline and centrifuged, and cytology is done on the pellet.

The size and character of the prostate can be evaluated via transrectal palpation using a gloved, lubricated finger. A normal prostate is symmetric, smooth, bi-lobed, and “walnut-shaped” with a dorsal median raphe. In severe cases of BPH, the cranial extent of the prostate may be difficult to palpate; it may be necessary to simultaneously palpate with the gloved finger, while concurrently placing upward pressure on the caudal abdomen to move the prostate back within reach.

Although BPH may not be radiographically apparent, survey abdominal radiographs may reveal cranial displacement of the bladder and dorsal displacement of the colon in affected dogs [5]. Ultrasonography reveals a homogenous parenchyma, with or without a cavitating cystic lesion [27].

A presumptive diagnosis of BPH is made based on a dog's history, physical examination findings, examination of prostate fluid, and prostate imaging. A definitive diagnosis of BPH is made with a transabdominal biopsy of the prostate. Common histopathologic findings include dilated acini surrounded by smooth muscle and fibrous connective tissue and the absence of inflammatory cells or organisms.

Dogs with BPH are treated only if they show clinical symptoms. One dog with clinical signs of BPH that was left untreated successfully impregnated bitches for 7 years. However, the hypertrophied prostate gland may be susceptible to ascending infection by normal urethral organisms, which can lead to prostatitis. Therefore,

treatment of BPH in valuable breeding dogs may prevent progression of prostatic disease and subsequent subfertility [5].

Castration is the recommended treatment for most dogs with BPH [28]. After castration, the prostate decreased in volume by 50% within 3 weeks and by 70–75% within 9 weeks; serum DTH concentrations decreased, and urethral bleeding ceased [29].

Estrogenic compounds, including diethylstilbestrol and estradiol cypionate, have been used to treat BPH. Since potential complications include thrombocytopenia, leukopenia, and fatal aplastic anemia, these compounds are not recommended [5]. Synthetic progestins, including megestrol acetate, medroxyprogesterone and chlormadinone acetate, have also been used to treat BPH [30]. However, as progestins and estrogenic compounds are not approved for use in male dogs in the United States, they are not recommended for the treatment of dogs with BPH [5].

The antiandrogen flutamide has been used in the treatment of BPH in research dogs. Romagnoli [22] reported that 5 mg/kg/day orally for 1 year did not alter libido or sperm production in dogs. In most countries flutamide is not approved for use in veterinary medicine, although it appears safe, effective and well tolerated in dogs [22]. In other studies, Win 49596, an androgen receptor antagonist, and FR146687, a steroid 5 α -reductase inhibitor, also reportedly decrease prostatic size in research dogs; however, neither is commercially available [31,32].

Finasteride, a synthetic steroid 5 α -reductase inhibitor, has been the focus of medical treatment of BPH in humans [33]. It decreased size of the prostate in dogs with BPH [25,34] and was successfully used to treat BPH in dogs at a dosage of 0.1–0.5 or 5 mg/kg for a 10–50 kg dog for 8–53 weeks [33,25]. Based on research at Washington State University [25], finasteride decreased serum DTH concentrations to baseline values. Additionally, it decreased prostatic size and semen volume, with no adverse effects on semen quality or serum testosterone concentrations. No side effects were reported with administration of finasteride in dogs treated for BPH [34]. In follow-up studies after finasteride treatment, there was no change in testicular weight, daily sperm production, or fertility [4,31]. Recent studies confirmed that finasteride can be used to reduce prostatic size in dogs with BPH without adversely affecting semen quality or serum testosterone concentration [25]. However, finasteride is not approved for use in dogs in the United States.

The use of a GnRH agonist is a new development in treatment of prostate disease [22,35]. These compounds

down-regulate GnRH receptors at the gonadotropes in the pituitary gland, suppressing the function of the hypothalamic-pituitary gonadal (HPG) axis, decreasing the release LH and FSH, and in turn decreasing concentrations of gonadal hormones (progesterone, testosterone) and their by-products. It is suggested that such a block to steroidogenesis can be utilized to control BPH, without side effects. Romagnoli [22] reported that prostate size decreased in parallel with a decrease in testosterone concentrations following GnRH agonist administration. Adult dogs were implanted with deslorelin (0.5–1.0 mg/kg body weight), prostate volume decreased >50% and serum testosterone had decreased 90% (relative to controls) at 6 weeks. However, once the treatment was discontinued, the prostate returned to its approximate pre-treatment volume by 48 weeks. Therefore, it was suggested that deslorelin was an appropriate treatment for BPH [22].

4.2. Prostate inflammation and infection

Prostatitis is an inflammation of the prostate gland, often due to bacterial infection. Prostatitis can occur at any age, but it is more common in older dogs with BPH; it is rare or nonexistent in castrated dogs due to atrophy of the prostate gland [24]. Dogs with prostatitis may have hematuria, hemospermia, or both. Cytology of the third fraction of the ejaculate may contain large numbers of leukocytes.

Bacteria associated with prostatitis are those that typically cause ascending infections of the urinary system of the female dog, including *E. coli*, *Klebsiella* sp., *Staphylococcus* sp., *Streptococcus* sp., *Proteus* sp., and *Pseudomonas* sp. Furthermore, *Mycoplasma* sp. and/or *Ureaplasma* sp. are also possible opportunistic pathogens. *Brucella canis* can also infect the prostate. Mycotic infections of the prostate gland occur rarely. Except in mild cases, it is usually difficult to collect an ejaculate. Culture of the third fraction of the ejaculate or urine obtained by cystocentesis is indicated. Urinalysis will reveal pyuria, hematuria, bacteriuria, and perhaps an increase in squamous epithelial cells. The urine culture will usually be positive; gram negative colony counts $>10^5 \text{ mL}^{-1}$ are suggestive of infection.

Bacterial prostatitis is treated with antibiotics with high lipid solubility [36], including enrofloxacin or trimethoprim-sulfamethoxazole. The treatment should be long-term (4–6 weeks), and follow-up evaluation is important. If BPH is also present (which is typical), it should be treated by castration or appropriate medical management, because the condition is likely to recur [24].

Some dogs with bacterial prostatitis may develop abscesses of the prostate gland. These abscesses can be life-threatening, as they can result in septicemia, endotoxemia, and localized peritonitis. A bacterial abscess of the prostate gland is a medical and surgical emergency, requiring rapid medical stabilization by treating septicemia and shock and surgical drainage [24].

4.3. Prostatic cysts

Prostatic cysts are usually incidental findings (detected during an ultrasonographic examination of the prostate) and are often asymptomatic. These cysts may be classified based upon their location as follows: (a) cysts associated with prostatic hypertrophy, (b) true retention cysts within the prostatic parenchyma, and (c) paraprostatic cysts outside the prostatic parenchyma [36].

Intra-prostatic cysts often occur in association with BPH or secondary to prostatitis. Paraprostatic cysts are usually located near the prostate. The origin of these cysts is obscure, but they may be remnants of the müllerian duct system (i.e. uterus masculinus). The cysts are often so large that they resemble a “second urinary bladder”. The distinct wall has a variable thickness and is occasionally mineralized. Laboratory examination of prostatic cyst fluid is not a common procedure, and there is the risk of inducing a needle tract infected with bacteria. However, if the dog is symptomatic and a large prostatic cyst(s) is the primary finding, aspiration, examination and culture of prostatic cyst fluid may provide useful information. Associated symptoms can include tenderness, lethargy, dysuria, hematuria secondary to cyst hemorrhage, and straining during defecation (due to compression of the rectum by a large cyst). These cysts usually do not interfere with prostate function. Medical therapy of prostatic cysts has not been extensively reported. If the cysts become so large that they obstruct flow of urine, surgical treatment may be considered. Corrective modalities could include cyst drainage by aspiration, cyst resection, marsupialization, and partial prostatectomy.

4.4. Prostatic neoplasia

Approximately, 5–7% of dogs with prostatic disease have prostatic neoplasia [24]. The most common neoplasm of the canine prostate is adenocarcinoma [24,36]. However, transitional cell carcinoma, leiomyosarcoma, and hemangiosarcoma have also been reported. Prostatic adenocarcinoma is most common in

older male dogs; it occurs in both intact and castrated dogs. Based on a retrospective study, castration may be a risk factor for development of this neoplasia [37], contrary to the popular belief that castration reduces the risk of prostatic carcinoma. More research is needed to clarify this apparent discrepancy.

The clinical presentation of the dogs with prostatic neoplasia is similar to other prostatic diseases, including tenesmus, bloody urethral discharge, hematuria and stranguiria. Additional clinical signs in more advanced cases are lumbar or caudal abdominal pain, rear-limb weakness, weight loss, anorexia, and cachexia. On transrectal palpation, the gland is typically enlarged and irregular, and it may be adhered to the floor of the pelvis. The majority of prostatic neoplasms are malignant. On ultrasound examination, the neoplastic prostate appears hyperechoic. Metastasis to the lumbar vertebrae and/or pelvis and to regional lymph nodes, or lungs, is common. In some dogs with prostatic adenocarcinoma, areas of calcification within the gland are observed. When prostate calcification is detected, it is usually associated with prostatic carcinoma. In radiographs, irregular bone formation on the ventral aspect of the lumbar vertebrae and/or the ileum in the presence of an enlarged, mineralized prostate indicates metastasis [36].

The prognosis for dogs with prostatic adenocarcinoma is poor, with typical survival of 1–2 months after diagnosis. The disease is usually diffuse within the gland, and has often metastasized prior to diagnosis. Surgical resection is not a good option for the dog, because it results in permanent urinary incontinence, and is unlikely to cure the cancer. Radiation therapy may improve the survival time, but local side effects such as colitis, urethritis and cystitis make this option less than ideal. Chemotherapy may be the best option, but current protocols are not very successful. If urethral obstruction occurs, a cystostomy tube is the most effective way to improve quality of life for the dog that is not yet debilitated by the disease. Euthanasia is often recommended.

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