

Hypothyroidism in canine reproduction[†]

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Abstract

Hypothyroidism is one of the most commonly diagnosed endocrine diseases in dogs. It has been implicated for many reproductive difficulties in breeding dogs; however, only a few studies have investigated the involvement of thyroid hormones in reproduction. Due to intricacies related to appropriate testing, breeding animals may be placed on thyroid supplementation without justification. The disease, testing, heritability, and animals that may need supplementation are discussed. Additionally, the assumption/appropriateness of breeding animals that are truly hypothyroid is questioned.

Keywords: Hypothyroid, reproduction, endocrine, infertility

Pathophysiology and diagnostic challenges

Hypothyroidism is the most common endocrine disease diagnosed in canine practice, although true disease prevalence is unknown.^{1,2} Over 90% of cases are due to an immune-mediated pathogenesis characterized by lymphocytic thyroiditis or idiopathic follicular atrophy.^{1,3} Rarely hypothyroidism is due to a secondary or tertiary pathogenesis, but those account for <5% of cases.³ Gonadectomized animals appear to be over-represented and in euthyroid animals circulating thyroid hormone concentrations decrease as dogs age. Disease onset is insidious and can take months to years before any clinical signs develop.³

Average age at onset of clinical signs is 7 years and clinical signs overlap with other endocrinopathies in many cases.^{1,3} Obesity is present in ~ 50% of cases, followed by dermatologic aberrations (present in 60-80% of dogs).³ Dermatologic conditions commonly include alopecia, seborrhea, poor hair coat, and lethargy or a dull mentation.^{1,3} Several breeds are at an increased risk of developing hypothyroidism, mainly, Golden Retrievers and Doberman Pinschers. Beagles and Borzois have heritable lymphocytic thyroiditis.^{4,5} Breeds that have a high incidence of thyroglobulin autoantibodies (TgAA) (antithyroglobulin antibodies) include Boxers, Dalmatians, Giant Schnauzers, Great Danes, Setters, and Old English Sheepdogs, among others.^{1,3-7}

Diagnosis should be based on serologic testing and not on clinical signs alone as there are many diseases and medications, or even breed differences, that contribute to altered circulating thyroid hormone concentrations. Accurate testing should be utilized before supplementation is considered. Both 3,5,3'-triiodothyronine (T3) and thyroxine (T4) are highly protein bound and subject to drastic changes in concentrations of albumin and thyroxin-binding globulin.¹ Many diseases can also falsely lower circulating T4 concentrations and yield a diagnosis of euthyroid-sick syndrome. Specific drugs can alter circulating serum concentrations of thyroid hormones; therefore, any animals being treated with sulfonamides, glucocorticoids, and/or phenobarbital should be tested after a 'washout' period, or if this is not practical, the results should be interpreted carefully.^{1,3} There are lower circulating T4 concentrations in specific breeds, including Greyhounds, Whippets, Scottish Deerhounds, Basenji, Alaskan sled dogs, and Sloughis; these breeds have breed-specific reference ranges.^{1,3,8-11} Importantly, euthyroid dogs have lower T4 concentrations at some time point during the day, a major consideration when testing is recommended.¹

Thyroxine concentrations are lower in >90% of hypothyroid dogs. Most general practitioners can use 'in-house' serum T4 concentration tests. This test is sensitive, but is not specific for canine hypothyroidism and should be avoided as a single test.^{1,3} The most accurate single test to diagnose hypothyroidism is free thyroxine (fT4) by equilibrium dialysis.³ Thyroid

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autoantibodies, and to a lesser extent nonthyroidal illness, do not affect fT4 concentrations. Combining serum concentrations of thyroid hormones increases success in identifying animals with true hypothyroidism. Using thyrotropin (TSH) information with T4 or fT4 typically yields a 98% specificity.^{1,3} In sighthounds, T3 concentrations may be useful because their T4 concentrations are typically outside reference ranges.³ Thyroglobulin autoantibodies (TgAA) form as the dog's immune system reacts to their thyroglobulin and are present in approximately 50% of all hypothyroid dogs.³ Animals that are positive for TgAA but with normal thyroid function tests should be retested annually, as they have a higher risk of actually developing clinical disease than do euthyroid dogs with negative TgAA.¹²

Reproductive manifestations

Hypothyroidism in humans has been studied extensively and is currently ongoing. There are known reproductive manifestations that affect both women and men. Reports include abnormal cyclicity or anovulation, infertility, loss of pregnancy in women, and loss of libido or fertility in men.^{13,14} Women who did not receive adequate supplementation of thyroid hormones or who have had impaired iodine intake during pregnancy had children with substantial effects,^{15,16} particularly impaired cognitive function. The relation between thyroid hormone supplementation and diet is being elucidated in women. The effect of thyroid hormones on both in vitro and in vivo pregnancy rates are also being studied. Men who were >35 years and subclinically hypothyroid had decreased clinical pregnancy rate when compared with their euthyroid counterparts.¹⁴ Although these findings are valid, it is important to notice that human and canine pregnancies are very different. Humans have higher concentrations of thyroxine binding globulins (TBG) and placental deiodinases; both drastically increase the metabolic demand for thyroid hormones during pregnancy.¹⁷ Humans also produce human chorionic gonadotropin (hCG) in pregnancy, which has substantial thyrotropic activity.¹⁷ Broad assumptions based on human literature surrounding hypothyroid disease and its reproductive effects in dogs should be avoided due to these differences.

Fewer studies were performed on dogs, but despite the lack of data, a plethora of reproductive diseases are 'blamed' on hypothyroidism. Reports have implicated hypothyroidism for cycle aberrations, abortion, infertility, and stillbirth.^{3,18-20} To date only a handful of prospective studies have been performed specifically highlighting the reproductive manifestations of hypothyroidism in female dogs. A review of 204 dog breeds suspected to have heritable hypothyroidism failed to demonstrate any significant difference in circulating thyroid hormone concentrations among normal, infertile, and subfertile male and female individuals.⁷ Additionally, a large prospective study that utilized fertile, previously proven mongrel female dogs, in which hypothyroidism was induced with ¹³¹I treatment, shed some light on pregnancy and hypothyroidism. During the short-term portion of the study, all dogs cycled normally, became pregnant and carried their litters to term.²¹ Furthermore, there was no difference in litter size, although pups born to hypothyroid dogs weighed less and experienced more periparturient mortality. Weight gain of pups was equal between the groups to day 28 postpartum. The increased periparturient mortality was attributed to possible prolonged uterine contractions that could be due to generalized muscle weakness in hypothyroid patients.²¹

A second article, from the same cohort, evaluated the effects of prolonged experimentally induced hypothyroidism on reproduction. All experimental animals were profoundly hypothyroid and had typical clinical manifestations of weight gain, hair coat changes, weakness, and lethargy.²² Control and hypothyroid female dogs were bred twice during this portion of the study, once without supplementation and once with levothyroxine supplementation. Many variables were monitored to document the effects of long-term uncontrolled hypothyroidism during pregnancy (2nd breeding) and the effects of supplementation and pregnancy after clinical signs were controlled (3rd breeding). The interestrus interval (IEI), pregnancy rates, and duration of pregnancy were not different between groups.²² Following the second breeding, only half of the hypothyroid dogs became pregnant, highlighting profound long-term effects of hypothyroidism.²² Ultimately, levothyroxine supplementation eliminated any differences between the groups at the 3rd breeding.²² A final study evaluated circulating thyroid hormones present in the hypothyroid female dogs from the 3rd breeding of the same cohort. No gestational adjustments in thyroid supplementation were required for inducing a euthyroid state due to no difference in thyroid hormone concentrations or progesterone concentrations between groups, which is drastically different from hypothyroid women.¹⁷

Another study evaluated dogs that had aborted their litters after 4th week of pregnancy. This study measured only T4 and progesterone and failed to conduct further diagnostics to work up the cause of abortion. This leads to only a weak argument for a direct effect of T4 being a singular cause of abortion.²³

Conflicting reports exist regarding hypothyroidism and its effects on male dog fertility. Specific colonies containing similar genetic makeup had both hypothyroidism and infertility.^{2,5,24} Due to the specifics of genetic makeup of these colonies, one might argue that the infertility observed may be due to limited genetic diversity rather than a direct effect of low circulating thyroid hormones. One 1997 study reported that induced hypothyroidism did affect male dog fertility but a later (2009) in vivo study reported no statistical difference in thyroid function between fertile and infertile dogs.^{7,25} Another 1999 study utilized induced hypothyroidic dogs and noted no change in libido, daily sperm output, motility parameters, nor sperm morphology between control and hypothyroid dogs.²⁶

A few major points from these studies are important. No experimental study to date has reproduced reproductive failure following an immunogenic hypothyroidism mechanism, the naturally occurring disease in canine populations. Manifestations of any reproductive failure have required elimination of all functional thyroid tissue within the animal. This raises the question of whether the reproductive effects observed are due to the lack of circulating hormones or a chronic inflammatory state produced by profound endocrine disease and associated endocrine disruption. Furthermore, many of the animals in the studies were obese, which is an independent cause of reproductive failure in many species. Despite these drawbacks, it is fair to conclude that primary hypothyroidism and its effects on reproduction in canine patients are only weakly associated. Hypothyroidism should be approached cautiously as a cause of clinical infertility or subfertility.

Heritability and testing breeding animals

Many breeds are labeled as 'at risk' for developing hypothyroidism. Consequently, there is a high suspicion that a heritable

and genetic component may be a factor in developing the disease. The insidious nature of the disease and difficulties surrounding its definitive diagnosis have left heritability studies as inconclusive. This leads to the conclusion that the underlying genetics are likely a polygenic trait that varies from one breed to another and that developing hypothyroidism is also heavily influenced by environmental factors.⁶ Penetrance of the offending alleles is also likely to have a role in the expression of clinical disease. Despite these drawbacks, there are testing mechanisms that help screen potential breeding stock and assist breeders and veterinarians in choosing animals less likely to pass hypothyroidism on to their offspring. The use of specific, accurate testing mechanisms is very important. The use of a single T4 or even T4 combined with TSH should be avoided in screening broodstock. A full panel including fT4 by equilibrium dialysis, T4, cTSH, TgAA, and T3/fT3 should be used. Animals that are exhibiting signs of concurrent disease should not be tested until the disease state has been resolved. Testing should begin around 1 year of age and should continue every 1–2 years while the animal is breeding or until the animal reaches 8–10 years of age. This allows for identification of animals that may develop subclinical disease over the course of their life, despite never having fulminant clinical signs. It is important to remember that hypothyroidism is a disease that is easily and successfully treated. Animals that may be TgAA positive and remain in the normal range of other thyroid function tests should not be eliminated from the breeding pool, because eliminating them can lead to diminished genetic diversity for many other traits. Breeding animals must be taken as a whole, and breeders should avoid ‘throwing the baby out with the bathwater’, especially for a disease that is so easily treated.

Levothyroxine supplementation

Only animals that had appropriate testing and elimination of all other potential causes of infertility should be considered for levothyroxine supplementation. Typically, these dogs have been bred several times, conceived, and failed to deliver or lost a large portion of their litter to resorption during the 4th to 6th week of pregnancy. Documentation of similar history with appropriate diagnostics, serial ultrasonographic examinations of the reproductive tract, infectious disease testing, complete blood count and biochemical profiles are warranted before considering supplementation. This includes a thorough history including pharmaceuticals used (preventatives and antibiotics), appropriate IEL, breeding method(s) and timing, fertility of the sire, genetic evaluation of the breeding pair, and any other comorbidities. Intrauterine cytology, culture and/or biopsy should be performed in early proestrus, positive results should be taken seriously (addressed and discussed), and automatic pharmaceutical treatment is avoided. If the animal is timed appropriately, bred to a proven, fertile sire and again fails to carry to term, then it is time to consider supplementation. Supplementing typically causes female dogs to be hyperthyroid, and this should only be done if a clear justification exists.

Supplementation needs to be fully discussed prior to implementation. This discussion should include the genetic possibility of needing exogenous hormone therapies to maintain pregnancy in their lines. Terminal, performance breeding is well accepted, but a kennel that is experiencing reproductive failure should carefully consider eliminating this type of animal as a brood female dog.

Once daily treatment of oral levothyroxine (0.02 mg/kg) is sufficient for supplementation. Treatment for female dogs

should start as soon as the veterinarian feels that they fit the criteria discussed above (during pregnancy) or at the beginning of her next estrous cycle and will be bred. All pregnancies in these dogs are considered high risk and should be monitored carefully and often. A tapered withdrawal over 2 weeks should be initiated immediately after whelping. Typically, these dogs do not have any other confounding factors, and are without evidence of endometritis, pyometra, or metritis, hypoluteoidism, or other causes of pregnancy failure. Breeders often demand supplementation well before a clear cause is identified; however, there is sufficient evidence that the thyroid gland must be profoundly affected before severe reproductive problems manifest. This provides a clear path to appropriate and science-based supplementation. There may be another mechanism in which thyroid supplementation will assist these specific cases, but the exact role has not been elucidated and is the very reason for caution. This calls for the judicious use of thyroid supplementation despite what is known in breeder community as ‘breeder lore’.

Conclusion

Hypothyroidism is a common disease of our canine population and is difficult to definitively diagnose. Furthermore, evidence of direct cause and effect of hypothyroidism and reproductive failure in a natural disease state is lacking. Reproductive veterinarians need to weigh all infectious, genetic, and husbandry causes of reproductive failure diligently and in a systematic approach before diagnosis and supplementation of thyroid hormones are implemented.

Conflict of interest

The author declares that she has no conflict of interest.

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