Recommendations on diagnosis and management of thyroid disease and the use of thyroxine in horses

EQUINE ENDOCRINOLOGY GROUP

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Recommendations on Diagnosis and Management of Thyroid Disease and the Use of Thyroxine in Horses

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Introduction

These recommendations were prepared as a practical guide for equine practitioners who are faced with interpreting blood thyroid hormone concentrations or assessing a horse that presents with goiter. While they represent the consensus of researchers who have studied thyroid diseases in horses, these recommendations are not peer reviewed.

Thyroid disease in horses is extremely difficult to characterize. Unlike most species, horses tolerate large swings in their thyroid hormone concentrations and can even live and reproduce when their thyroid glands are removed. Naturally-occurring hypothyroidism and hyperthyroidism are extremely rare in adult horses, and congenital hypothyroidism is only occasionally detected in foals. Clinical signs that have been historically associated with thyroid disease are vague and nonspecific with the exception of the presence of a goiter. Goiter is defined as an enlarged thyroid gland for any reason. In adult horses it is most often caused by thyroid cysts or tumors, most of which are non-functional.

The Equine Endocrinology Group (EEG) is composed of experts in the field of equine endocrinology who provide advice in the form of written guidelines to help veterinary practitioners diagnose and manage equine endocrine disorders. Guidelines are updated every two years or when new information becomes available ~~and can be found on the EEG web site: http://sites.tufts.edu/equineendogroup.~~

Thyroid disease in adult horses

Hypothyroidism is commonly misdiagnosed in adult horses. The medical definition of hypothyroidism is an inability of the thyroid gland to produce thyroid hormones when stimulated. Confirmed cases of hypothyroidism are so rare in adult horses that it is hard to describe a naturally occurring form of the disease. Even thyroidectomized horses appear remarkably normal and remain active; with cold intolerance, low body temperatures, bradycardia, and haircoat abnormalities as the primary clinical findings.[1-4] Despite the lack of evidence for primary hypothyroidism in adult horses, hypothyroidism is commonly, yet erroneously, diagnosed in the United States when low triiodothyronine (T3) or thyroxine (T4) concentrations are found on screening panels. Many physiological states (cold exposure, prolonged exercise and others), diseases, and medications can cause blood T3 and T4 concentrations to decrease (Table 1). Practitioners are strongly advised to determine if other factors affecting thyroid hormone concentrations are present before making a diagnosis of hypothyroidism. These recommendations provide a guide for interpreting blood thyroid hormone concentrations and assessing horses with goiter, and provides answers to frequently asked questions about thyroid disease in horses.

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Interpretation of low thyroid hormone concentrations in adult horses

Diagnostic laboratories routinely measure and report plasma or serum total T3 (tT3) and total T4 (tT4) concentrations because this information is used by small animal practitioners to diagnose thyroid disorders in cats and dogs. Thyroid hormone concentrations may also be included on equine serum biochemical profiles or endocrine panels. When low tT3 and/or tT4 concentrations are reported for a horse, it is a common misconception that this confirms the diagnosis of hypothyroidism. This is incorrect, as in almost all cases low tT3 and tT4 concentrations reflect the body's normal response to other factors. It is important to remember that the hypothalamic-pituitary-thyroid axis is a dynamic endocrine system and "point in time" measurement of circulating thyroid hormone concentrations provides no information about rates of production or secretion of thyroid hormones by the thyroid gland. A diagnosis of hypothyroidism is only appropriate when results of a thyroid function test confirm that the thyroid gland cannot respond adequately to stimulation. *Simply put, hypothyroidism should not be diagnosed in horses based on blood thyroid hormone concentrations alone. For this reason, it is the recommendation of this group that thyroid hormone concentrations be removed from equine biochemical profiles.*

PRACTITIONER'S TIP: ***Blood thyroid hormone concentrations alone should not be used to diagnose hypothyroidism in horses and are not a sufficient reason to begin replacement therapy.***

There are many potential explanations for low tT3 and tT4 concentrations, and a flow chart for interpreting results is provided in Figure 1. In all but the rarest of situations, the explanation for this finding is not hypothyroidism, but one of the many factors affecting thyroid hormone concentrations. For example, low tT3 and/or tT4 concentrations occur in horses receiving phenylbutazone. The list of causes of low blood tT3 and tT4 concentrations has lengthened as we have learned more about thyroid hormone responses in horses, and **Table 1** provides current information.

When hypothyroidism is suspected in an adult horse, a stepwise diagnostic approach is recommended. The first step is to consider if there is a plausible explanation for low tT3 and/or tT4 concentrations in the patient other than hypothyroidism. If the answer is no, the second step is to measure free T4 (fT4) concentration by the equilibrium dialysis method. Free thyroxine is the portion of total blood thyroxine that is not protein bound, and is the active form of the hormone. The equilibrium dialysis method is the only accurate way to determine its concentration. This may mean sending the sample to a referral laboratory that offers this specific test. If the fT4 concentration is low, then the third and final step is to perform a thyroid function test by performing a thyrotropin-releasing hormone (TRH) stimulation test. A diagnosis of hypothyroidism is reached if the pituitary-thyroid axis fails to respond to TRH administration, and treatment with levothyroxine might be justified at this point.

Although hypothyroidism is very rare in adult horses when the diagnostic criteria described above are applied, it is acknowledged that we have more to learn about thyroid hormone responses in horses. It remains possible that situations exist where the thyroid gland response is inadequate for the physiological stress or disease encountered, even though the horse has normal results when a thyroid function test is performed. This question cannot be answered at present and more research is required to explore individual variability in thyroid hormone concentrations and determine if suboptimal thyroid responses affect the health of the animal.

Unfortunately, measurement of endogenous Thyroid Stimulating Hormone (TSH) is not available in horses. It is possible that if one could assess TSH concentrations in addition to tT3 and tT4 concentrations, many challenging cases would be more accurately evaluated.

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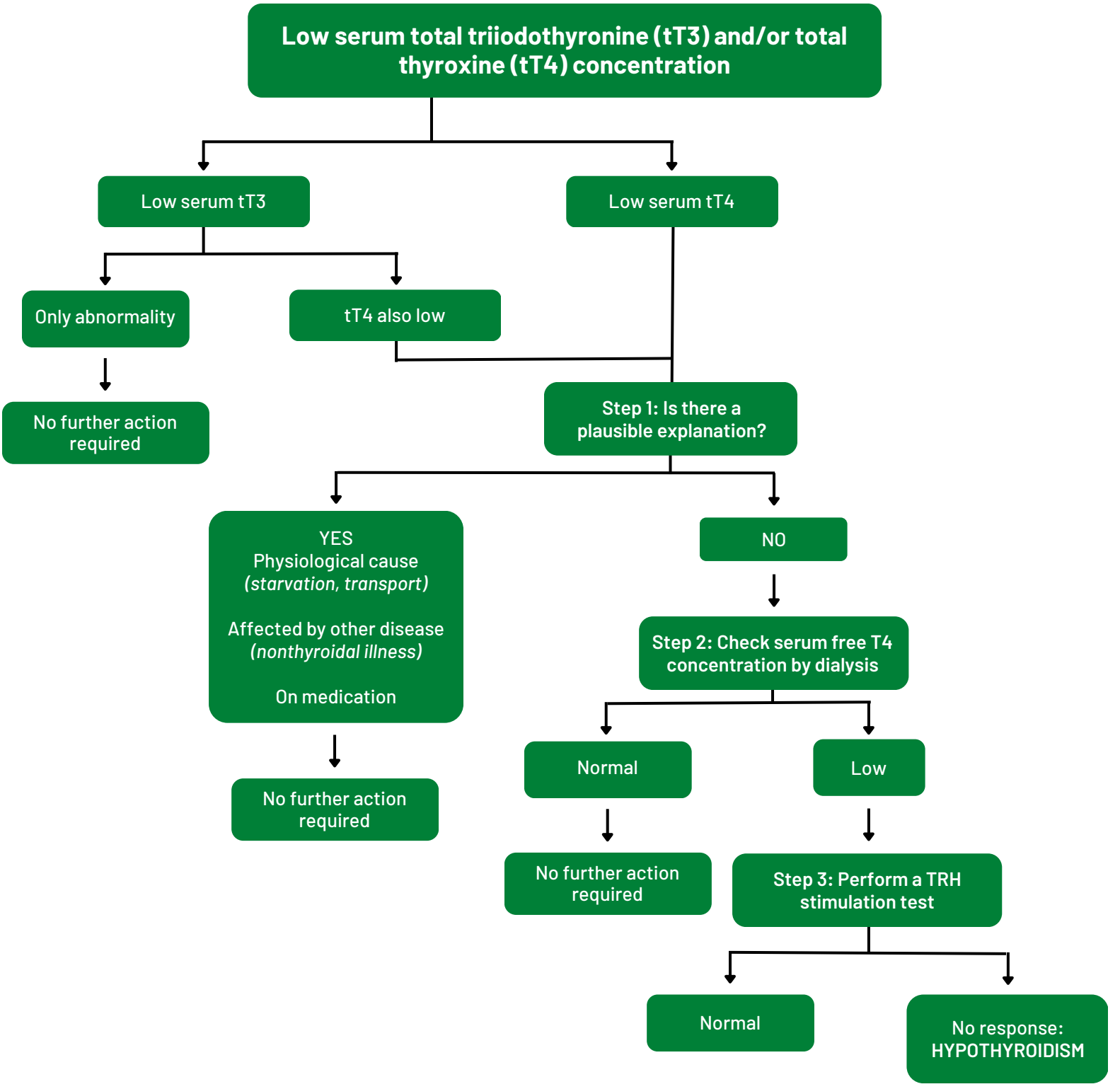
Figure 1 – Flow chart for interpreting low thyroid hormone concentrations in adult horses



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Interpretation of high thyroid hormone concentrations in adult horses

Naturally occurring hyperthyroidism has been reported in horses secondary to functional thyroid tumors. Although cases are rare, clinical signs include weight loss, hyperexcitability, polyphagia, tachycardia, polydipsia, and goiter.[5-8] Blood tT3 and tT4 concentrations are often 2-3 times higher than normal in affected horses. Affected horses have responded well to hemithyroidectomy once the affected gland was identified although complications including laryngeal hemiplegia can develop. Consequently, upper airway endoscopic examination is recommended before surgery is pursued. Another treatment can be administration of propylthiouracil to suppress thyroid hormone production.[5]

Hyperthyroidism can also be iatrogenic, when horses receive excessive amounts of thyroxine as a supplement. This can produce excitability, weight loss, and cardiac arrhythmias. Although thyroid hormone supplementation is a tool used in management of horses with insulin dysregulation (see EEG EMS recommendations), supplementation should be judicious and horse owners should be informed that the in these instances thyroxine is not being used to treat hypothyroidism.

Assessment of goiter in adult horses

Enlarged thyroid glands (goiter) in adult horses are most often caused by benign adenomas with cysts as a less common cause. These enlarged glands do not affect thyroid function and simply require monitoring over time. In rare cases when they may grow so large the airway or esophagus can become compressed, hemi-thyroidectomy can be curative. However, surgery can be complicated by nerve injury leading to upper airway dysfunction. Functional thyroid gland tumors (adenocarcinomas) are rare and usually accompanied by clinical signs of hyperthyroidism (e.g., weight loss or agitation on rare occasions).

C-cell tumors of parathyroid tissue within the thyroid gland are another type of thyroid gland neoplasia. Serum concentrations of calcium, ionized calcium, phosphorus, and PTH may be analyzed to assess if a C-cell tumor is functional.

PRACTITIONER'S TIP: Ultrasound examination is the best way to evaluate an enlarged thyroid gland. Tumors may be solid or have a characteristic cystic appearance. BIOPSY OF THE GLAND IS NOT RECOMMENDED as the thyroid is an extremely vascular organ that bleeds profusely and percutaneous biopsy samples can be non-diagnostic.

Thyroid Function Testing

The TRH stimulation test is used to assess the hypothalamus-pituitary-thyroid axis. The protocol is to collect serum for baseline serum tT3 and tT4 measurements, administer 1 mg TRH intravenously, and then measure the serum tT3 concentration two hours later and serum tT4 concentration four hours later. Greater than 1.5-fold increases in blood tT3 and tT4 concentrations are normally detected although any increase is evidence that the gland is responding to the TRH and should exclude a diagnosis of primary hypothyroidism. Side effects of TRH administration include coughing, muscle fasciculations, chomping, and exhibition of the Flehmen response. These side effects are only seen in some horses, and they resolve within a few minutes. Thyrotropin-releasing hormone can be purchased from compounding pharmacies as a 1 mg/mL solution for intravenous injection in the United States.

PRACTITIONER'S TIP: One can diagnose PPID at the same time using TRH. In this instance, additional blood could be collected into an EDTA tube at baseline and exactly ten minutes later, and plasma adrenocorticotropic hormone concentrations are measured. For more information see the latest EEG PPID recommendations.

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Frequently asked questions about thyroid disease and diagnostic testing

Why don't serum concentrations of T3/T4 reflect thyroid function?	The hypothalamus-pituitary-thyroid axis works to set the basal metabolic rate. It reacts to an animal's health and environmental state on a minute-to-minute basis. Downregulation of thyroid secretion occurs in response to a myriad of factors (see **Table 1**). For this reason, low blood thyroid hormone concentrations are most often the body's reaction to the need to downregulate resting metabolic rate, not an indication of abnormal thyroid gland function.
What are the clinical signs of hypothyroidism in adult horses?	Unlike most species, a functioning thyroid gland is not necessary for life in horses. This is one reason hypothyroidism is considered rare in equids and is difficult to diagnose in adult horses. Clinical signs of naturally occurring hypothyroidism cannot be listed for this reason and we are only able to describe the physical characteristics of thyroidectomized horses. These animals have a sparse, coarse hair coat, bradycardia, and a consistently low body temperature.
What about the relationship between equine metabolic syndrome and hypothyroidism?	It was once thought that hypothyroidism was the cause of clinical signs we now attribute to equine metabolic syndrome (EMS). Low serum tT3 and tT4 concentrations are detected in many EMS horses and ponies, and this is to be expected given the endocrine and metabolic disturbances that are components of this syndrome. We can therefore think of EMS as a nonthyroidal illness, and blood tT3 and tT4 concentrations are low for this reason. It is important to note that none of the clinical signs historically attributed to hypothyroidism such as obesity, regional adiposity, laminitis, anhidrosis, or decreased fertility have been described in thyroidectomized horses and horses with EMS have normal thyroid function test results. As explained below, levothyroxine can be administered at a high dose for 3-6 months to accelerate weight loss in obese EMS horses, but this is not evidence of hypothyroidism.
What should be measured when assessing the thyroid gland?	Serum tT3 and tT4 concentrations are measured by most laboratories, and are included in a full serum biochemical biochemistry profile by some laboratories. When results are received, little importance should be attached to detecting a low tT3 concentration if the tT4 concentration is normal. However, finding a low serum tT4 concentration requires further investigation and a fT4 as measured by equilibrium dialysis should be performed. This requires submission of a serum sample to a laboratory that offers this more specialized test. The Veterinary Diagnostic Laboratory at Michigan State University (East Lansing, MI) and the Cornell Animal Health Diagnostic Center Endocrinology Laboratory (Ithaca, NY), offer measurement of serum free T4 (fT4) concentrations by dialysis. If the fT4 concentration is low, thyroid function testing is recommended.
Can TSH be measured in horses?	Unfortunately, measurement of endogenous thyroid stimulating hormone (TSH) concentrations is not commercially available for equine serum. There is no cross reactivity between antibodies used in assays to measure human and canine TSH and equine TSH; consequently these tests cannot be used.
What is euthyroid sick syndrome?	This is a condition in which serum concentrations of thyroid hormones are low in animals who have nonthyroidal systemic illness but who actually have normal thyroid gland function. Current evidence suggests that changes in thyroid secretion are an adaptation to reduce energy expenditure and to activate the innate immune response. The underlying illness should be addressed; thyroid hormone replacement is not indicated.

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Table 1 – Documented causes of low thyroid hormone concentrations in horses with normal thyroid function

Note: These lists are not exhaustive.

Cause	*Evidence*
Illness	Sick euthyroid syndrome[6, 7]
Species	Horses have lower thyroid hormone concentrations than donkeys[8]
Sex	Stallions have lower thyroid hormone concentrations than mares[9]
Age	Thyroid hormones are highest at birth and decrease throughout an animal's life[10]
Season	Thyroid hormone concentrations are more commonly increased in cold seasons than in hot seasons[11]
Time of day	Thyroid hormone concentrations are generally higher in the afternoon than in the morning[12]
Fasting and refeeding	A negative energy balance will result in downregulation of the resting metabolic rate and circulating thyroid concentrations[13]
Drug administration	Phenylbutazone and other drugs may decrease circulating thyroid hormone concentrations[14]
Exercise	Prolonged (endurance) exercise can lead to decrease in circulation thyroid hormone concentrations[15]

Table 2 – Documented causes of short-term increases in thyroid hormone concentrations in horses with normal thyroid function

Cause	*Evidence*
Transport	Transport may increase thyroid hormone concentrations[16]
Diet	High carbohydrate or fat meals may cause increased thyroid hormone concentrations[17]

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Thyroid disease in foals

Unlike adult horses, hypothyroidism in foals is well documented and results in a cluster of clinical signs. Most of the clinical signs are characteristic of dysmaturity, although prognathism is unique to hypothyroidism. Hypothyroidism appears to develop *in utero* in late pregnancy and can lead to prolonged gestation times (at times > 1 year). Because the skeleton is one of the main tissues affected and it develops during late gestation, affected foals are born with varying severity of skeletal immaturity, notably forelimb contracture and incomplete ossification of carpal and tarsal cuboidal bones. Another essentially pathognomonic skeletal abnormality is mandibular prognathism (monkey jaw). Depending on the severity of skeletal immaturity, affected foals can be managed successfully if confined and provided supportive care but euthanasia is often elected. Proper nutrition of the mare is the best way to prevent congenital problems. Pregnant mares should not receive high iodine supplements, be kept on fescue pasture in late gestation, or be allowed access to plants that contain goitrogens.

Signs of Hypothyroidism in Foals
Delayed ossification of carpal and tarsal bones
Mandibular prognathism (monkey jaw)
± Goiter
Respiratory distress
Dysmaturity

Assessing thyroid function in foals

T4 and T3 values are high in newborn foals, up to ten times adult values. These decrease quite rapidly over the first few weeks of life, then continue to decrease slowly over the life of the horse. It is important to assess thyroid hormone values in foals by comparing concentrations to age-matched controls.

Thyroid hormone in premature and ill foals

Premature foals have lower thyroid hormone concentrations than foals born at term. Septic and sick foals have lower thyroid hormone concentrations than healthy foals.[18] This may be a manifestation of euthyroid sick syndrome. The effects of thyroid hormone replacement in sick or premature foals has not been studied.

Figure 2 – Thyroid hormone concentrations in 20 normal foals over the first month of life.

Shaded gray areas represent the normal reference range in adult horses.
From: Breuhaus, B. J Vet Intern Med 2014;28:1301[18]

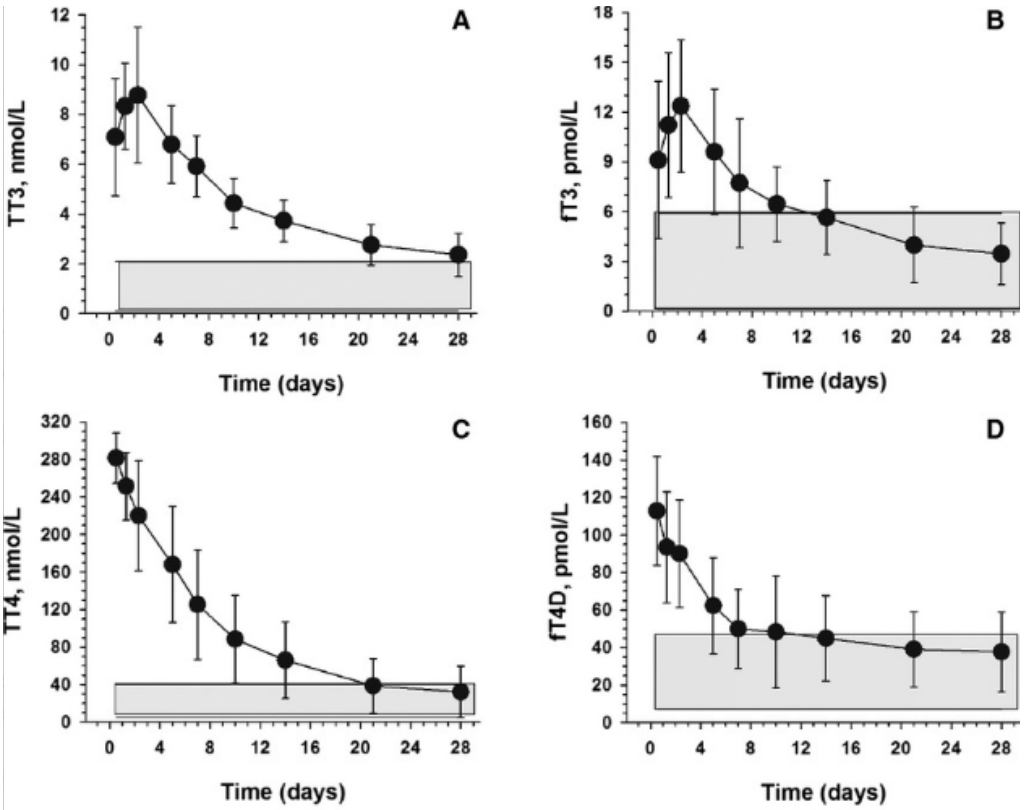

Table 3 - Hypothyroid syndromes in foals

Cause	*Evidence*
CHD – Congenital hypothyroidism and dysmaturity[19]	Found most commonly in northwestern portions of North America, although seen sporadically worldwide. Cause not definitively known, but ingestion of mustard plant glucosinolates implicated. There seems to be a seasonal influence on severity of CHD, with foals born later in the spring or summer having longer gestational lengths and more severe skeletal defects including mandibular prognathism.
Excess consumption of iodine during pregnancy[20]	Foals typically born with goiter. Kelp and other seaweed containing supplements are extremely high in iodine and should not be fed to pregnant mares.
Fescue ingestion during pregnancy[21]	Low thyroid hormone concentrations accompany dysmaturity in foals born to mares who ingest *Acremonion coenophialum* fungus-infected fescue.
Idiopathic	Foals may be born with goiter, but with no other clinical signs of thyroid disease. Goiter usually resolves over time with no treatment.

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Measurement of thyroid hormones

T4 and T3 can be measured via an immunochemiluminescent assay (Immulite), ELISA, or RIA. The normal ranges using these three techniques vary and cannot be directly compared. When evaluating a horse's values, it is imperative that the individual laboratory's normal ranges be used. Equilibrium dialysis should be used when measuring free T4. Consult your diagnostic laboratory if there are any questions about testing methods or results.

Thyroxine as a pharmacologic agent

Thyroxine is often used in the treatment of horses with non-thyroidal conditions. Practitioners should bear in mind that exogenous thyroid hormone supplementation will result in down regulation of endogenous thyroid gland function.

Equine Metabolic Syndrome (EMS)
Thyroxine can be used to aid in the management of EMS and insulin dysregulation. Giving 2X the replacement dose (0.1 mg/kg po SID, 4 teaspoons for a 500-kg horse; 12 mg per teaspoon) increases weight loss and often lowers insulin concentrations in horses with EMS. Thyroxine should only be given as part of a complete management protocol including a low carbohydrate diet and caloric restriction, and only for 3-6 months. Once the horse has reached an ideal weight, the thyroxine supplement should be slowly decreased over 2-4 weeks until the horse is weaned off completely. For further information on the management of EMS, see the EEG recommendations.

Poor performance
Horses that are poor performers or picky eaters are often placed on thyroid supplement. This may result in a horse that has an increased appetite and is more spirited, giving the false impression that it is helping performance. Despite this, actual athletic performance is decreased due to thyroxine-induced decreases in cardiac function. Supplementation of thyroxine in extra-physiologic amounts can result in atrial fibrillation and other cardiac arrhythmias.[22] For this reason, thyroxine supplementation IS NOT RECOMMENDED for the treatment of horses with poor performance.

Disclosures

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