



4075 Iron Works Parkway • Lexington, KY 40511  
Phone: 859-233-0147 • Fax: 859-233-1968  
e-mail: [aaepoffice@aaep.org](mailto:aaepoffice@aaep.org)

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By Emily A. Graves VMD, MS, Dipl. ACVIM

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Equine endocrine disorders have been recognized for decades. However, only more recently have they become a focus of significant research on diagnosis and the efficacy of treatment. The most common endocrine disorders dealt with today by equine practitioners and owners are pituitary pars intermedia dysfunction (PPID, a.k.a. Cushing's syndrome), metabolic syndrome (EMS), insulin resistance (IR) and suspected hypothyroidism. In general, the endocrine system is composed of several organs which produce hormones that control many body functions. These organs include the hypothalamus, pituitary gland, thyroid gland, parathyroid glands, adrenal glands, pineal body and the reproductive organs (ovaries and testes). The pancreas is also on this list; it has both hormone production and digestion duties. Compared to people and companion animals, endocrine disorders appear to occur less frequently. While other diseases are known to occur in equid species, such as diabetes insipidus and hyperthyroidism, they are extremely rare findings. Thus, the remainder of this discussion will focus on the most common endocrine problems in horses and ponies, namely PPID, metabolic syndrome and IR. In this presentation, the aim is to provide clear, concise definitions of these illnesses and review current practices in diagnosis, treatment and long-term management. The first section reviews clinical signs and management, while the second section describes diagnostic testing options for these disorders.

## **Clinical Presentation and Management**

### *Pituitary Pars Intermedia Dysfunction (PPID)*

Pituitary pars intermedia dysfunction is the most common endocrine disorder in equine species. The acronym PPID is preferred in the veterinary community because it provides a more accurate name. Cushing's disease in people and dogs differs in some important aspects. The affected portion of the pituitary gland is different, and thus use of the human medical term "Cushing's" can be misleading. The pituitary gland dysfunction in equids stems from overgrowth, meaning hyperplasia or tumor, of certain cell types within the gland's pars intermedia. These cells are hyperactive or present in high numbers, and thus lead to production of abnormally high levels of many pituitary hormones. This list includes adrenocorticotrophic hormone (ACTH), melanocyte stimulating hormone ( $\alpha$ -MSH),  $\beta$ -endorphin, and other products of a large precursor hormone, called **Pro-Opiomelanocortin** or POMC. While not all of the effects of these hormones are known, some like ACTH are better understood.

Specifically, ACTH overstimulates a horse's cortisol synthesis by the adrenal glands. The hyper-cortisolemic state leads to the long list of outward problems in the affected animal. The more common signs observed in PPID-affected equids are:

- 1) Failure to shed fully
- 2) Long, sometimes curly, haircoat – this can begin as long hairs along the jaw line and "feathers" near the fetlocks
- 3) Chronic infections
- 4) Repeated laminitis episodes, sometimes with associated hoof abscesses
- 5) Excess or inappropriate sweating
- 6) Increased water intake and urination, called polyuria/polydipsia (PU/PD)
- 7) Lethargy
- 8) Loss of muscle mass (later in process, if horse is untreated) – typically noticed over the back and hind quarters, as well as the "pot-bellied" appearance

- 9) Infertility or lack of estrus cycles
- 10) Abnormal mammary gland development

Some laboratory test abnormalities seen in PPID cases are low lymphocytes, increased neutrophil counts, and intermittent high blood sugar. The veterinary community has not yet determined the cause and effect for every PPID sign. One understood consequence is the effect of long-term high blood cortisol concentrations. Cortisol is called a “stress” hormone and leads to immune system suppression over time. This suppression can result in chronic infections in PPID-affected horses or ponies. In addition, chronic elevations in cortisol are thought to be related to a state of high insulin secretion and greater potential for insulin resistance to develop. Insulin resistance will be discussed further in the following section on EMS.

Many of the clinical signs of PPID can be managed by the owner using some routine steps, including:

- 1) Frequent bedding changing or constant outdoor turnout (to avoid excessively wet stalls)
- 2) Body clipping throughout the year
- 3) Frequent bathing for the excess sweating, especially in hot weather
- 4) Consistent monitoring for signs of infection and appropriate treatment

However, the most disheartening and damaging clinical sign of PPID is laminitis. Typically, this complication has a slow, insidious onset. Hoof changes and pain develop gradually and are often intermittent, but typically leading to chronic foot pain and anatomic changes. This disease is thought to be related to cortisol and other hormonal effects on glucose (aka sugar) action on the tissues of the hoof wall. It is an active area of research, as many of you know. Once a diagnosis has been made, the challenge for owners of PPID horses is to find and develop a “team” of people to aid in managing, not curing, both PPID and laminitis. This team ideally includes one’s veterinarian, a farrier, and the horse’s caretakers. Farrier therapies for PPID-associated laminitis will not be discussed further.

Additionally, an integral part of PPID management is medical treatment. While none of the medications I will discuss are curative, they can provide substantial alleviation of clinical signs that is incredibly important to the treated animals and owners. The most widely used drug is **pergolide**. This is the generic name of the drug which is a dopamine agonist. That substance is naturally produced in all of our bodies, and it serves to decrease some of the hormone production by the pituitary gland. This drug has never been approved for use in horses. In fact, it is one of many human medications that are used in an extra-label, legal manner by veterinarians for their equine patients. Very recently, the availability of this human product was put into question after the Food and Drug Administration (FDA) announced that the drug would no longer be marketed in the United States. Fortunately, through the combined efforts of the American Veterinary Medical Association, the American Association of Equine Practitioners, the FDA and thousands of horse owners, the FDA recently decided to allow bulk availability of pergolide for pharmaceutical compounding use in the horse. Regarding pergolide’s efficacy, several studies have addressed its usefulness in PPID-affected equids and shown significant improvements in hair coat, frequency of urination and drinking, frequency of infections and laminitis bouts, and many laboratory test results.

Another drug which works at the level of the pituitary gland and brain is **cyproheptadine**. This drug is a serotonin antagonist and works indirectly to achieve similar effects as pergolide. Some of the same studies described earlier were comparison studies of horse groups treated with either pergolide or cyproheptadine. These studies suggest that cyproheptadine is not as effective in improving the clinical signs of PPID. However, it has been used with success by many practitioners and owners, and seems to aid those animals with minimal response to pergolide alone. So although the combination of the two drugs is more expensive, this combination can be a very useful treatment for some equine patients.

**Bromocriptine** is another medication that mimics the actions of dopamine, like pergolide. It has been used around the world to treat equine PPID cases. However, it is poorly absorbed and has been associated with severe side effects in many patients, including poor milk production in pregnant or lactating mares and diarrhea. Thus, this drug is rarely used for therapy.

**Trilostane** is a medication which decreases cortisol production through direct effects on the adrenal gland. It is not available in the United States at this time, but has been used in human medicine and small animal veterinary medicine overseas for many years. More recently, equine researchers in Great Britain assessed its

use in equine patients. While the number of horses treated with this drug is relatively small, the initial studies did show reversal of some clinical signs in PPID-affected horses. It should be noted as well that not all PPID cases have hyperplasia of the adrenal glands, and thus the drug cannot be expected to help all cases.

In the herbal remedy field, some veterinarians and owners have reported positive results following use of **chaste berry supplements**. Commercial product names include Evitex™ and Hormonize™. Anecdotal reports exist that chaste berry is helpful to PPID horses. However, a comparison study concluded that an herbal product containing chaste berry (*Vitex agnus castus*) had no beneficial effect on horses with PPID compared to a group treated with pergolide (the most common medication for PPID in horses). It should be noted that standardization of herbal remedy contents is not required and therefore it is virtually impossible to know exactly what one is buying.

To summarize, PPID is a disease of older equids that can be managed, but not cured. Chronic infections and laminitis tend to be the most detrimental and frustrating clinical manifestations of the disorder. Thus, early recognition and regular veterinary and farrier care are imperative to help one's horse or pony maintain a good quality of life.

### *Insulin Resistance and "Metabolic Syndrome"*

Equine Metabolic Syndrome is a recently described collection of clinical abnormalities which shares some characteristics with PPID. Both of these disorders alter cortisol metabolism. It is thought that EMS results from excess production of active cortisol primarily in fat cells or adipose tissue. The pituitary gland functions normally in patients with this disorder. Understandably, while the underlying causes of EMS and PPID may be different, the resulting clinical problems are very similar, including abnormal fat deposition (along the crest, over the tail head, and in geldings' sheaths) and laminitis. With more recent study of the syndrome, experts agree that the term EMS should be used only when the following, three diagnostic criteria are met:

1. insulin resistance (IR),
2. history of or active laminitis, and
3. excess fat depositions in typical regions (i.e. neck crest, fat pads at the base of tail).

Insulin resistance is a term used to describe the condition in which various body tissues fail to respond appropriately to insulin. In a classic scenario, the individual has both abnormally high blood sugar and blood insulin concentrations. Once the pathologic state of IR develops, poor utilization of glucose from the diet and intermittent high blood sugar occurs (similar to Type 2 diabetes mellitus in people). Diets that are higher in carbohydrates exacerbate this state because they stimulate further insulin production when eaten. The possible mechanisms behind IR in horses are numerous and can be discussed with your veterinarian. A major concern with IR is that it appears to be linked to pasture-associated laminitis in horses and ponies. Thus, when IR is identified or suspected in a horse, veterinarians often suggest methods which may help a horse's insulin sensitivity. This typically includes diet changes and an increase in regular exercise. As an aside, although IR is not identified in all horses with PPID, it can be an associated endocrine problem for many equine PPID cases as well.

Management of horses and ponies with EMS focuses on therapy for laminitis and dietary adjustments with the aim of limiting the stimulus for insulin production. Unfortunately, because of the abundance of high carbohydrate-content commercial feed options, diet supervision can be extremely difficult for owners. In order to decrease this stimulus for insulin secretion, an alternate feeding regimen with a *low* glycemic index is recommended for these patients. Fortunately, this goal is becoming easier to achieve in today's world. Glycemic index signifies the degree to which a certain food raises blood sugar and insulin levels in the body. Molasses-based diets, such as sweet and senior feeds, as well as oats and barley have high glycemic indexes. Low glycemic index feeds include Bermuda grass hay, rice bran and beet pulp. Other hays, such as timothy and alfalfa, have moderate glycemic indexes. An important recommendation is to feed grass hay or other feed sources which are low in water-soluble carbohydrates (WSC) or non-structural carbohydrates (NSC). Forage analysis of your hay is strongly encouraged to accurately determine the WSC/NSC content of one's hay. NSC content below 12 percent is suggested for IR horses and ponies, in both EMS and PPID patients. Also, if more calories are needed, fat sources, such as vegetable oil or rice bran, are excellent choices instead of grains and feeds with high molasses content. Higher fiber content in the daily diet also is encouraged. This can be found in beet pulp and many commercially produced pelleted feeds.

Regarding medical therapy, some veterinarians have begun to look at the use of trilostane (described in the PPID treatment section) in EMS cases. Again, this drug is not available in the U.S., but researchers argue that decreasing cortisol production by the adrenal glands may help reduce clinical signs in EMS patients. Addition of oral antioxidants, vitamin E specifically, has also been recommended (5000-7000 units per day). Before making any treatment decisions, additional therapy or supplement use should always be discussed with your regular veterinarian. Also, with any PPID and EMS patient, regular health check-ups are critical to long-term care. This includes the performance of basic blood work, dental care and regular foot/hof trimming and care.

### *Hypothyroidism*

On the topic of hypothyroidism in equine species, the veterinary community knows that true primary hypothyroidism in horses is quite *uncommon*. What is occurring far more often is a phenomenon in which another body illness causes the thyroid hormones to be under-produced by the thyroid gland. Also, many common medications (ex. phenylbutazone) and normal daily events (ex. changes in daylight hours, ambient temperature) quickly effect blood levels of thyroid hormones. Because low thyroid hormone levels are often observed in many PPID and EMS animals, thyroid hormone supplementation has become commonplace. While giving thyroid hormone supplementation to a horse with low levels may “normalize” the hormone measurement, it may not be addressing the underlying problem or is treating a non-existent problem.

Once a horse begins daily thyroid hormone therapy, it is expected that he/she will lose weight and likely have more energy. This is because thyroid supplements provide extra thyroid hormone, the hormone which determines the animal’s metabolic rate. Thus, the more thyroid hormone, the higher the metabolic rate, meaning weight loss and a higher activity level, etc. Thyroid supplementation can be quite useful to aid in weight loss in an overweight horse. However, because true hypothyroidism is so rare in horses, experts now suggest consideration of using such supplements only as a short-term therapy to achieve weight loss goals with a patient. In summary, horse owners should know that primary hypothyroidism in horses is rare, and that low thyroid hormones measured are typically a result of another disease process or factor.

## **Diagnostic Test Options**

### *Pituitary Pars Intermedia Dysfunction*

For PPID, there are a variety of diagnostic tests available. The options fall into two categories: dynamic tests, which assess responsiveness of the horse’s endocrine glands, and single sample tests, which serve as “screening” tools for PPID.

Dynamic test options include the dexamethasone suppression test (DST), the diurnal cortisol rhythm, the thyrotropin releasing hormone (TRH) stimulation test, and a combined DST/TRH stimulation test. Of these, the DST is probably the most widely accepted. In this test, a patient’s cortisol level is measured first, then a test dose of exogenous (from an outside source) steroid is given. A second cortisol measurement is taken 15 to 19 hours after this test steroid dose. A diagnosis is made when the second cortisol measurement fails to go below a set cortisol concentration. Some limitations of this test are that it requires multiple veterinary visits, and that the test dose of steroid *may* worsen a horse’s laminitis (if present). It should be noted that occurrence of this latter concern is not well documented.

Single sample test options include measurement of resting ACTH concentration, serum insulin concentration, and other pituitary gland products. One caveat is that ACTH can be elevated outside this normal range during certain months, namely in early fall. It is theorized to be due to seasonal effects on normal pituitary hormone production. What this means is that a normal horse may have an elevated ACTH during this time of the year, and be wrongly diagnosed with PPID. Also, after collection of blood from a horse, the sample requires special handling. If possible for an owner, it is often a smart choice to have both the DST and ACTH measurement performed on your horse or pony.

Lastly, it must be emphasized that none of these tests are 100 percent sensitive and specific for diagnosis of PPID. In horses with more advanced PPID, the common sign of the long, curly haircoat can be as good as a blood test in making the diagnosis. The bigger challenge now is making a PPID diagnosis at a *much* earlier

stage in the disease process. That is a current, primary focus of many equine endocrine disease researchers.

### *Metabolic Syndrome and Insulin Resistance*

For Equine Metabolic Syndrome, testing options are still debated as the equine medical community learns more about this syndrome. To diagnose EMS, presence of the previously described clinical changes and blood tests are used. A single test to identify increased cortisol *in fat tissue* does not yet exist. The primary and most consistent laboratory abnormality is a high serum insulin concentration. In addition, because of the shared traits of animals with EMS and PPID, it is important to rule out a diagnosis of PPID. A distinguishing feature between EMS and PPID is the result of an overnight dexamethasone suppression test. EMS patients have normal responses, i.e. normal cortisol suppression following a dose of dexamethasone, whereas PPID patients have abnormal DST results, i.e. lack of cortisol suppression. Similarly, endogenous plasma ACTH concentration is normal in EMS cases and elevated in most PPID patients. Also, because laminitis is often the first complaint, assessing coffin bone position with foot radiographs is very important.

In addition, in order to evaluate a horse or pony for IR, it is recommended to measure the horse's resting insulin concentration, as well as perform an insulin-glucose sensitivity test. This test requires several blood samples to be collected over a relatively short period of time. It can be done in the field, but is often not practical for the busy, ambulatory veterinarian. Thus, many veterinarians are using their test of choice for PPID combined with serum glucose and serum insulin measurements to evaluate a horse or pony for EMS. While the results can be frustrating and not point to an obvious diagnosis, they are still useful tools. Veterinarians recognize that many horses and ponies fit an "inconclusive" category where PPID or EMS cannot be diagnosed with certainty. That said, it is often suggested to repeat diagnostic tests in horses suspected of having PPID. It is possible that at some times, his hormone levels are abnormal, and at other times, they are normal.

### *Hypothyroidism*

A single sample test for thyroid hormone levels is *not* the diagnostic test of choice for hypothyroidism in horses. The preferred test is called the TRH Stimulation test and this requires multiple blood samples to be collected. Also, it is often difficult to perform because the TRH needed for the test can be very difficult to find. It is not a commercially available "test kit." Thus, unfortunately, assessing a horse's thyroid gland responsiveness is a challenge in today's world. It is more easily done at a university veterinary hospital. While single sample thyroid hormones tests can tell one if a horse's levels are in or out of range, they do not tell one if true thyroid illness is present. Another single sample test that is a standard in assessing thyroid function in people, cats and dogs is thyroid stimulating hormone (TSH). Unfortunately again, this blood test is not commercially available for horses. It is another goal in the equine veterinary research community.

## **More Metabolic Disease Information**

### *Hyperlipemia/Hyperlipidemia*

A metabolic disorder that can be life threatening and involves insulin resistance is "fatty liver" or, more appropriately, hyperlipemia/hyperlipidemia syndrome. When equine animals get sick from any type of illness, and if they are off feed for lengthy time period, many complications can result, one of which is hyperlipemia/hyperlipidemia. We know that overweight patients, ponies, miniature horses, and donkeys and mules are predisposed to this condition. In the state of a negative energy balance, these affected animal's livers start to store excessive amounts of fat, as the body tries to mobilize fat stores for energy. One factor is that various substances in the blood stream make these animals insulin resistant and thus unable to properly use blood sugar for energy. Hence, the "release of fat" from body stores and the subsequent overload of the liver. As stated, this can be a fatal disease if the primary illness is not treated aggressively.

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4075 Iron Works Parkway • Lexington, KY 40511

Phone: 859-233-0147 • Fax: 859-233-1968

e-mail: [aaepoffice@aaep.org](mailto:aaepoffice@aaep.org)