CHAPTER 11

Hyperadrenocorticism (Pituitary Pars Intermedia Dysfunction) in Horses

Catherine McGowan

Pathogenesis

- Equine hyperadrenocorticism is almost invariably associated with pituitary dysfunction, a condition referred to as pituitary pars intermedia dysfunction (PPID).
- As the name suggests, it affects the pars intermedia of the pituitary gland not the pars distalis.
- It causes a loss of dopaminergic inhibition of the pituitary pars intermedia resulting in increased pituitary peptide production including α-melanocyte-stimulating hormone (α-MSH), adrenocorticotropic hormone (ACTH), and β-endorphin.
- PPID is a neurodegenerative disease associated with aging, most closely related to human Parkinson's disease.

Classical Signs

- It is a common (20%) problem of horses, ponies, and donkeys 15 years of age and older with no breed or sex predilection.
- A variable combination of clinical signs is seen, the most common of which is hirsutism.
- Other signs include polyuria and polydipsia, hyperhidrosis, muscle catabolism, and weight redistribution resulting in a loss of epaxial musculature and a potbellied appearance.
- Secondary infections and/or delayed wound healing are commonly encountered.
- Laminitis is frequently the most devastating consequence and may necessitate euthanasia.

Diagnosis

- Hirsutism is pathognomonic for PPID but diagnosis should be confirmed in all horses where treatment is initiated in order to have baseline endocrine values for monitoring purposes.
- Basal ACTH concentration or the low-dose dexamethasone stimulation test are most commonly used.
- ACTH or α-MSH response to thyrotropin-releasing hormone or domperidone can also be used.

Clinical Endocrinology of Companion Animals, First Edition. Edited by Jacquie Rand.

- Resting blood insulin and glucose concentrations are nonspecific but are recommended for monitoring purposes.

Treatment

- Dopamine agonists—pergolide mesylate is the drug of choice.
- Management of the horse including attention to hooves, teeth, deworming and clipping the hair coat, as well as clinical and endocrinological follow up are critical to the success of treatment.

I. Pathogenesis

A. The pathophysiology of PPID is **different from that of hyperadrenocorticism in other species**:

1. It is **almost invariably associated with pituitary dysfunction**, hence the name pituitary pars intermedia dysfunction (PPID). The condition has also been referred to, sometimes misleadingly, as equine Cushing's disease/syndrome, pituitary/hypophyseal/chromophobe adenoma, pars intermedia adenoma/hyperplasia, diffuse adenomatous hyperplasia of the pituitary, and pituitary-dependent hyperadrenocorticism. The preferred name pituitary pars intermedia dysfunction or PPID will be used throughout this chapter:
   a. Unlike Cushing's disease in dogs and humans, adrenocortical hyperplasia and hypercortisolemia are not consistent findings in horses with PPID.
   b. Only one case of adrenal gland–dependant equine Cushing's syndrome has been reported.
   c. Iatrogenic hyperadrenocorticism has also been reported but is much less common than PPID.
2. As the name suggests, PPID affects the pars intermedia of the pituitary gland:
   a. The pituitary gland (hypophysis) is comprised of two lobes: the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). The anterior lobe is further divided up into three parts; the *pars intermedia*, *distalis*, and *tuberalis*.
   b. When the pituitary gland is viewed histologically, three distinct areas can be appreciated, the pars nervosa (or neurohypophysis), the pars distalis, and the pars intermedia. The **part of the pituitary gland affected in the horse with PPID is the *pars intermedia*** (Figure 11.1).
   c. The pars intermedia is comprised entirely of the melanotrope cell type that synthesizes and processes a range of proopiomelanocortin (POMC) peptides. The melanotrope processes the parent POMC peptide further than the pars distalis so that the range of peptides produced are different from the pars distalis and include alpha-melanocyte-stimulating hormone (α-MSH), corticotrophin like intermediate peptide (CLIP), beta endorphin, and gamma-lipotropin. While POMC processing is markedly elevated, the relative proportions of peptides released from affected horses appears unchanged when compared with normal horses (Figure 11.2).
   d. Excessive hormone production leads to **hyperplasia** of that part of the pituitary gland which **may or may not then progress to adenoma formation** (Figure 11.3).
3. PPID involves a **loss of dopaminergic inhibition** of the pituitary pars intermedia:
   a. The pars distalis is well vascularized and receives releasing and inhibitory factors from the hypothalamus that control secretion.
   b. The pars intermedia is poorly vascularized and relies on neurotransmitters released from axons from the hypothalamus to control secretion, especially tonic inhibition by dopamine, mediated by dopaminergic D2 receptors on the melanotropes.
   c. The loss of tonic inhibition by dopamine mediated by the D2 receptor is responsible for excess pars intermedia activity and PPID.
4. PPID is a **neurodegenerative disease associated with aging**, most closely related to human Parkinson's disease:
   a. This is a factor that is important to convey to owners of affected horses as older terms such as pituitary adenoma or tumor may imply to owners that this condition is untreatable or that the prognosis is hopeless.

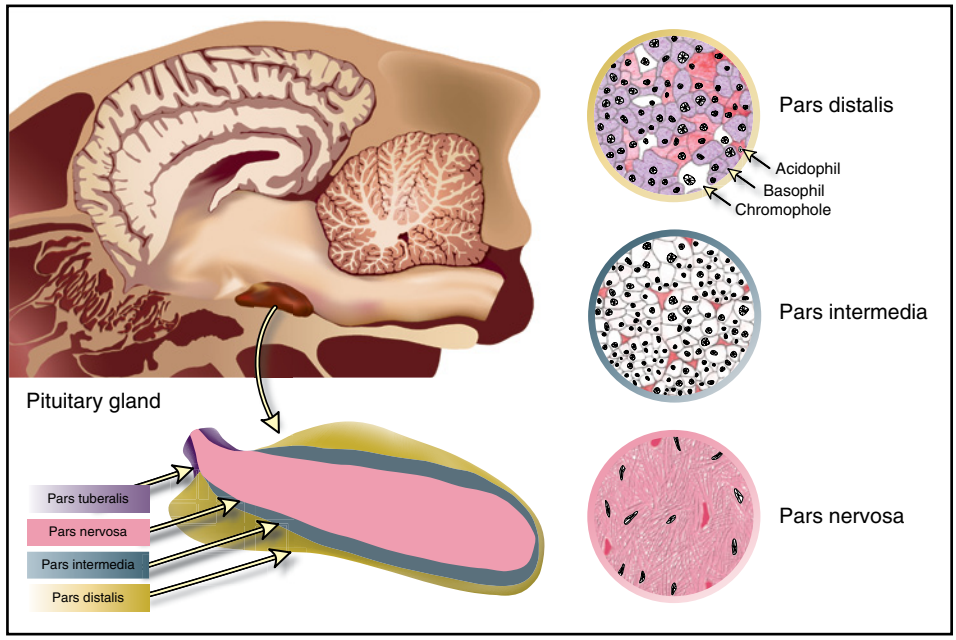

Figure 11.1 Equine pituitary anatomy and histology. (Photo courtesy of Cathy McGowan.)

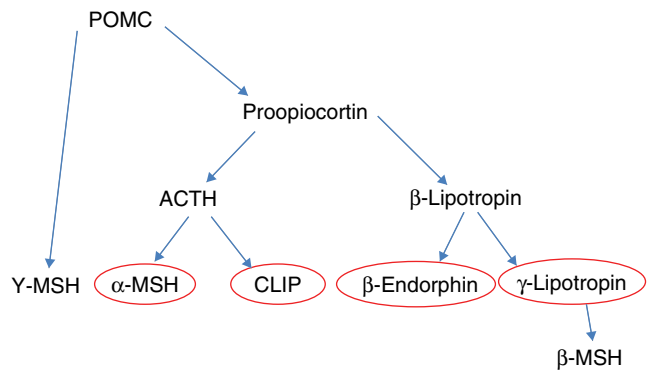

Figure 11.2 Proopiomelanocortin processing by pars intermedia melanotropes. ACTH, adrenocorticotropic hormone; CLIP, corticotrophin like intermediate peptide; MSH, melanocyte-stimulating hormone; POMC, proopiomelanocortin.

b. In studies of pituitary glands, there was a marked reduction in dopamine (to <12% of the control value) in affected horses compared with controls, but no change in serotonin concentrations between horses with PPID and control horses.

c. Immunohistological studies of pituitary glands of horses with PPID have shown that there is a marked reduction (to <20% of the control value) in tyrosine hydroxylase, a marker of functional dopaminergic neurons, and a 50% reduction in the cell bodies of the dopaminergic neurons compared to controls, as in Parkinson's disease.

d. Further, studies have shown an increased oxidative stress marker, 3-nitrotyrosine, and expression of alpha-synuclein in horses with PPID with both of these also found to occur in patients with Parkinson's disease.

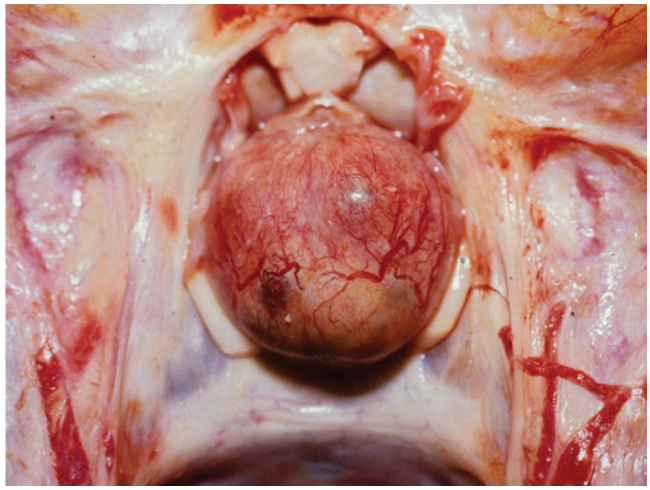

Figure 11.3 Enlarged pituitary gland post mortem in a horse. (Image courtesy of Prof. Derek Knottenbelt.)

Table 11.1 Mean age, clinical signs, and their frequency of occurrence in eight case series of horses with pituitary pars intermedia dysfunction.

Clinical sign	Heinrichs et al. (1990)	Hillyer et al. (1992)	Boujon et al. (1993)	van der Kolk et al. (1993)	Couetil et al. (1996)	Schott et al. (2001)	Donaldson et al. (2002)	McGowan and Neiger (2003)
Total number studied	19	17	5	21	22	77	27	20
Mean age (years)	19	20	18	21	21.5	23	19 (median)	19
Hirsutism	47%	94%	100%	100%	95%	83%	59%	100%
Laminitis	NR	82%	NR	24%	59%	52%	74%	80%
Weight loss or redistribution	NR	88%	60%	38%	50%	47%	33%	65%
Lethargy	NR	82%	20%	NR	41%	36%	19%	95%
Polyuria/polydipsia	26%	76%	NR	NR	32%	34%	7%	55%
Hyperhidrosis	NR	59%	60%	5%	14%	33%	29%	30%
Bulging supraorbital fat	NR	12%	40%	19%	9%	30%	26%	50%
Concurrent infections	21%	66%	40%	19%	36%	NR	30%	35%

NR = not recorded.

II. Signalment

A. PPID is a **common condition,** affecting approximately 20% of horses, ponies, and donkeys 15 years of age and older with **no breed or sex predilection:**

1. The **average age of diagnosis is 15–20 years** (Table 11.1).
2. The main risk factor for development of PPID is increasing age.

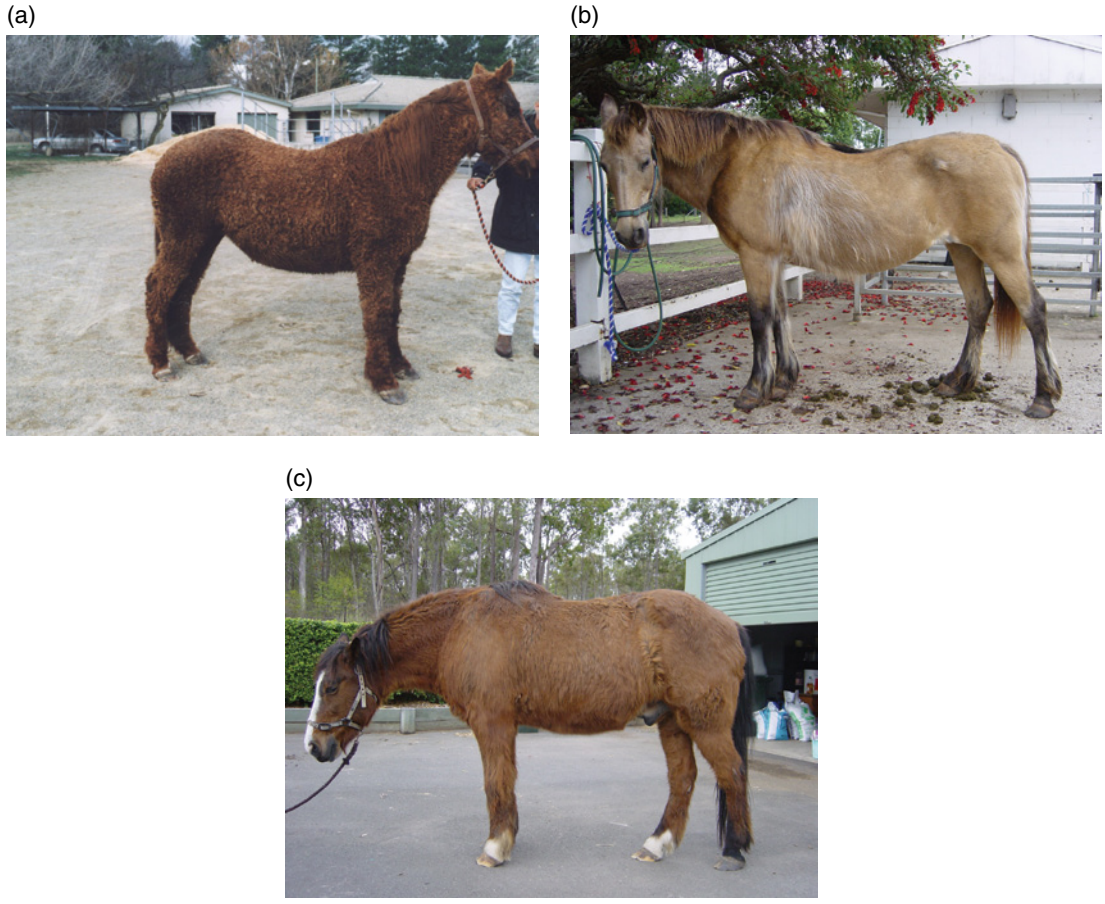

Figure 11.4 Hirsutism is the most common clinical sign in horses with PPID.

3. PPID is very rare in horses <10 years of age.

B. Despite earlier clinical case series reporting a seemingly increased proportion of ponies affected, ponies are not considered to be at increased risk. Ponies may appear overrepresented because:

1. People may be more likely to keep ponies for longer than horses due to easier management.
2. Hirsutism is often more noticeable in pony breeds.

III. Clinical Signs

A. A **variable combination of clinical signs** may be seen (Table 11.1):

1. The clinical syndrome falls across a spectrum of advancing severity associated with advancing disease.
2. The total number of clinical and historical signs of PPID increases in proportion with increasing plasma concentrations of the pituitary peptides ACTH and α-MSH.
3. A similarly **variable spectrum of pituitary pathology** is described from focal or multifocal hypertrophy or hyperplasia, to diffuse adenomatous hyperplasia, to adenomatous hyperplasia with microadenomas, to adenoma formation.

B. **Clinical signs** are hallmarked by **hirsutism** (excessive hair growth):

1. An owner-reported **history of delayed shedding or a long hair coat is the most significant historical finding** associated with PPID.
2. Hirsutism is not a normal feature of aging and is **pathognomonic for PPID**.
3. Hirsutism may range from delayed shedding each year, uneven hair coat with patches of alopecia, to a permanent long or even curly hair coat (Figure 11.4).

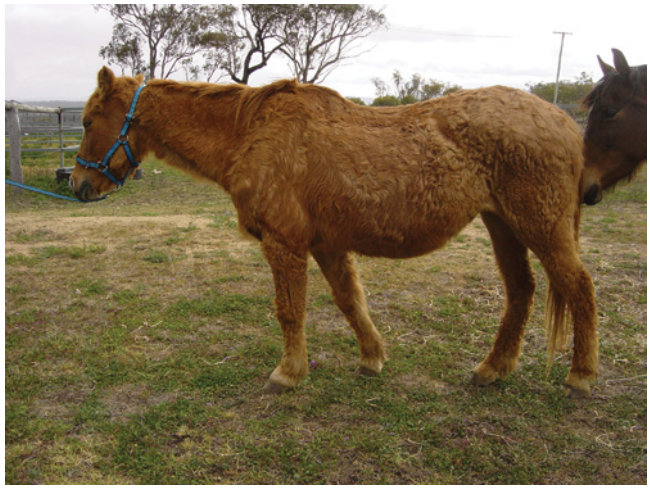

Figure 11.5 Muscle catabolism and weakness, with a potbelly and "sway back" appearance.

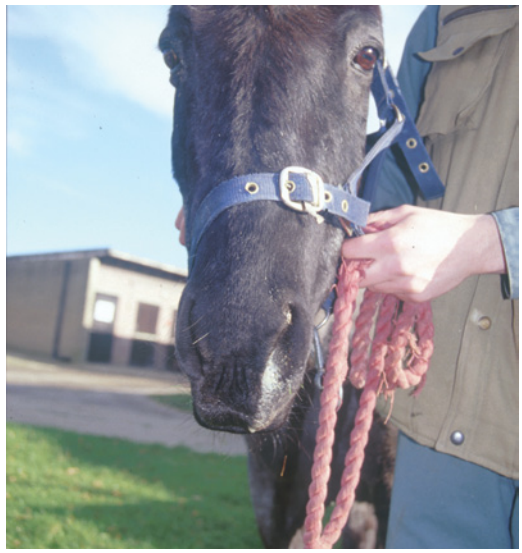

Figure 11.6 Sinusitis in this horse secondary to reduced immunity associated with PPID.

C. Despite the relatively low proportion of ACTH among POMC peptides released from the abnormal pars intermedia, **many of the clinical signs are attributed to hyperadrenocorticism:**

1. These include **polyuria and polydipsia** probably associated with direct effect of cortisol on antidiuretic hormone (ADH) production, although likely to be exacerbated by osmotic diuresis in hyperglycemic horses.
2. **Muscle catabolism** and weight redistribution:
   a. Horses usually appear **underweight, with loss of muscle over their back and a potbellied appearance**, attributed to the catabolic effects of hypercortisolemia (Figure 11.5).
   b. These signs are also associated with atrophy of type II muscle fibers, typical of steroid-induced myopathy as found in other species.
3. **Susceptibility to infections and reduction in healing,** for example, oral ulcerations, skin infections, periodontal disease, and sinusitis (Figure 11.6):

Figure 11.7 Styrofoam pads support this aged mare with PPID with severe (Grade 3) laminitis.

Figure 11.8 Pony demonstrating marked hyperhidrosis.

a. Unexplained periodontal disease, sinusitis, or recurrent infections in the aged horse should alert practitioners to the possibility of PPID.

4. **Recurrent or chronic laminitis,** most likely via the induction of insulin resistance secondary to the prolonged hyperadrenocorticism (Figure 11.7):
   a. Laminitis is frequently the most devastating consequence and **may necessitate euthanasia.**
   b. Laminitis in an aged horse without evidence of systemic illness or history of a feeding accident should be investigated in every instance for an underlying endocrinopathy (equine metabolic syndrome and/or PPID).

D. **Other clinical signs** may be attributable to other POMC peptides. However, the effects of other peptides secreted from the pars intermedia are not well known; neither are the effects of compression of the pars nervosa or pars distalis which may occur in some horses:

1. **Lethargy** is often attributed to excess β-endorphin activity.
2. **Hyperhidrosis** (excessive sweating) may be associated with catecholamine effects from the adrenal medulla, as a result of hirsutism reducing thermoregulatory capability or even due to the effects of compression of an enlarged pituitary gland onto the thermoregulatory centers (Figure 11.8).

3. Effects from an adenoma or enlarged pituitary on the brain stem are rare, although blindness has been reported:
   a. Anatomically, effects on the optic chiasm would be most likely from an enlarged pituitary gland (Figure 11.3), although further extension from an adenoma would be very unlikely.
   b. Seizures have been rarely reported in horses with PPID but the cause of the seizures has not been demonstrated to be due to the pituitary disease.

E. PPID causes a combination of clinical signs, especially lethargy and wasting, which are often considered indicative of a poor quality of life. However, these clinical signs have been consistently and successfully reversed by medical therapy.

F. **Clinical Pathology:**
   1. **Routine hematology and biochemistry are not useful in the diagnosis of PPID** as horses with PPID have no significant difference from age-matched normal horses:
      a. A stress leukogram, as seen in dogs, is not present.
      b. Aged horses, irrespective of whether they have PPID or not tend to have a relative lymphopenia.
      c. Inflammatory changes, if present, represent concurrent illness rather than the effects of hypercortisolemia.
   2. Routine hematology, serum biochemical analysis, and urinalysis may, however, provide valuable information about concurrent problems in an aged horse.
   3. **Routine hematology and biochemistry are also useful in the assessment and monitoring** of a horse with PPID with respect to **prognosis and response to therapy**.

IV. Diagnosis

A. Diagnosis of PPID is based on **history, clinical signs, and laboratory findings:**
   1. A **variety of diagnostic laboratory tests is available** but one limitation is that a gold standard antemortem test has yet to be identified. A definitive diagnosis may be achieved via postmortem examination in combination with clinical signs but this is of limited value to the practicing clinician.

B. It is important to consider the **reasons for diagnosis**, before deciding on a diagnostic protocol:
   1. **Aims of diagnosis:**
      a. To determine the need for treatment.
      b. To obtain prognostic information.
      c. To obtain baseline information in order to monitor the response to therapy.
      d. To differentiate from insulin resistance or equine metabolic syndrome.

C. **To determine the need for treatment:**
   1. If the reason for diagnosis is to **initiate and potentially monitor therapy**, then the method of diagnosis needs to be **most accurate** as treatment is expensive and lifelong.
   2. There are basically **two types of endocrine tests, basal and dynamic.**
   3. **Basal tests** are those that can be obtained with a **single sample** and are popular with veterinarians and clients due to **simplicity and reduced cost**, especially considering that testing may need to be repeated regularly following diagnosis:
      a. However, the benefits may be partially offset by the **reduction in sensitivity and specificity of diagnosis.**
   4. **Basal plasma ACTH concentration is currently the best option for a basal diagnostic test:**
      a. Sensitivities and specificities of >80% have been reported with a single cutoff value, with increased sensitivities and specificities >90% if seasonally adjusted reference ranges are used instead of a single cutoff value.
      b. **ACTH concentrations will increase in the autumn months**, with horses with PPID potentially having more pronounced increases.
      c. Some laboratories are now able to correct for the seasonal effects on ACTH and can provide altered diagnostic ranges for samples collected during this period.
      d. **Cutoff values** for diagnosis of PPID using basal plasma ACTH concentration will **vary depending on the assay used**, but, for example, for the Immulite® 1000, a value of 6.5 pmol/L (29.7 pg/mL) can be used as a cutoff for non-autumn months (>80% sensitivity and specificity), or 10.3 pmol/L (47 pg/mL) for autumn months (>90% sensitivity and specificity).

Table 11.2 Protocol for the low dose dexamethasone suppression test in horses.

- Collect a baseline serum blood sample followed by injection of 40 µg/kg dexamethasone intramuscularly.
- Collect a second serum sample between 18 and 24 h later and submit both to a laboratory for cortisol analysis. (Heparinized plasma samples can also be taken.)
- Cortisol is reasonably stable so both samples can be submitted as whole blood together, although it is pertinent to chill the samples (in a refrigerator).
- Normal horses show suppression of cortisol concentration of around 70–80% from baseline.
- Following administration of dexamethasone, affected horses have serum cortisol >40 nmol/L (1.45 µg/dL) from a baseline of around 100 nmol/L (3.62 µg/dL) while normal horses have suppression to <20 nmol/L (0.72 µg/dL).
- The "gray zone" in horses that suppress between 20 and 40 nmol/L (0.72 and 1.45 µg/dL) is difficult to interpret. Horses with high baseline values (>150 nmol/L (5.44 µg/dL)) usually have slightly less suppression and values less than 40 nmol/L are considered a normal suppression in this case. However, if in doubt, the test should be repeated or a basal adrenocorticotropic hormone concentration determined to help confirm the result.

e. ACTH is **labile** and the EDTA plasma samples should be separated and chilled within 3 h of collection, frozen within 12 h, and sent frozen to the laboratory. Plasma samples must not be kept in glass tubes as the ACTH is adsorbed onto glass.

f. This can be achieved in practice provided you take a pipette, plastic storage container, and cooler with ice packs with you (many laboratories provide collection packs). Blood can be collected in **an EDTA vacutainer, allowed to separate by gravity, and separated and chilled on ice within an hour.** It is advisable to check with your laboratory for any additional requirements they may have before collecting the sample.

5. **Basal α-MSH** may offer some advantages over basal ACTH as it is **specific to the pars intermedia** and not part of the adrenocortical axis (less affected by stress), but **is well correlated to ACTH in the field setting.**

6. **Dynamic endocrine testing** can provide **much greater diagnostic sensitivity and specificity** over simple measurement of basal hormone levels because they evaluate the integrity of endocrine regulatory feedback loops:

   a. **The low-dose dexamethasone suppression test has the highest reported sensitivity and specificity for the diagnosis of PPID.** When samples are collected 20 h apart, the test has been reported to approach 100% sensitivity and specificity (Table 11.2).

   b. The aim of the test is to **detect a failure of suppression of cortisol following the administration of dexamethasone** in horses with PPID.

   c. The rationale is that the ACTH and resultant adrenal cortisol production from affected horses are not affected by negative feedback. The pars intermedia is not affected by negative feedback, so affected horses fail to show a suppression of cortisol following administration of the exogenous glucocorticoid, dexamethasone.

   d. The test is affected by season, with the **potential for false-positive diagnoses during the autumn months.**

   e. The dexamethasone suppression test is **not affected by the time of day;** however, frequently it is convenient to perform an overnight test starting the afternoon before.

7. **Other dynamic tests** include the combined dexamethasone suppression/thyrotropin-releasing hormone (TRH) stimulation test and ACTH or α-MSH response to domperidone or TRH. These tests may offer increased diagnostic capability but are **not considered as first choice for field testing.**

8. Risks of dynamic endocrine tests:

   a. Some veterinarians and horse owners have raised concern about the possibility of exacerbating laminitis or inducing an attack of laminitis due to administration of dexamethasone.

   b. In the author's opinion, there is little doubt that excessive prolonged doses of corticosteroids can cause laminitis, particularly in a predisposed horse. However, the risk of the dexamethasone suppression test is minimal, and the benefits outweigh the risks. The dose given is low, less than half a single therapeutic dose, and given only once.

D. To obtain prognostic information and to obtain baseline information in order to monitor the response to therapy:

1. A horse with unequivocal hirsutism and three or more clinical signs of PPID may not require a diagnostic test to determine the need for treatment. However, prior to commencement of treatment, **baseline and prognostic tests should be obtained.**
2. **Insulin is the most important prognostic test** and will **correlate with laminitis:**
   a. PPID horses with high insulin (>1305 pmol/L [188 µIU/mL]) are more likely to develop laminitis and not survive 2 years compared to those with low to moderate elevations (<430 pmol/L [62 µIU/mL]).
   b. **Fasting samples** in horses that are managed with defined feeding periods are ideal, with one option being to collect the sample prior to the morning feed after an overnight fast of 6 h or to collect at 12 pm midday after the morning feed has been removed at least 4 h before.
3. **Blood-glucose concentration is also useful for prognostic purposes:**
   a. Blood glucose concentration is not very sensitive as a diagnostic test as **not all horses with PPID develop hyperglycemia;** however, **those that do have hyperglycemia often have more advanced disease,** possibly with additional disease stress and/or pancreatic exhaustion.
4. **ACTH concentration** has been correlated with the number of clinical signs of PPID and so **very high values** (except during the autumn) can be considered a **poor prognostic indicator:**
   a. ACTH concentration should decrease on pergolide therapy and can be used to adjust the dose if improvements of ACTH do not occur.

V. Differential Diagnoses

A. In cases where hirsutism is not apparent or laminitis is the primary clinical sign, it is important to differentiate PPID from **Equine metabolic syndrome** (see Chapter 20), both of which are associated with insulin resistance:

1. Dynamic or basal tests of pituitary peptides or the dexamethasone suppression test will be the best way to differentiate the two syndromes (see above).

B. In the absence of hirsutism, other clinical signs suggestive of PPID may be explained by a number of differential diagnoses:

1. Polyuria and polydipsia may be caused by neurogenic or nephrogenic diabetes insipidus, psychogenic polydipsia, or hyperglycemia of various origins (pancreatic disease, pheochromocytoma).
2. Weight loss and muscle wasting may be associated with dental disease, parasitism, or other age-related conditions.

VI. Treatment

A. There are several factors to consider regarding if and when to treat:

1. **Medical therapy does improve quality of life of affected horses.**
2. All owners should be informed and given the option of treatment.
3. **General preventive care and improved husbandry** by owners as an adjunct to medical therapy is **important** including hoof care, regular deworming, clipping, and dental care.
4. **Attention to diet is also important.** Horses with PPID are aged and potentially in a catabolic state so it is important to provide a balanced diet with **adequate high quality protein and to supplement for trace minerals and vitamins.** Large reductions in caloric intake are not recommended, although **ensuring PPID horses are not overfed** so as to remain/become fat is important.

B. Many veterinarians and owners will wait until clinical laminitis develops; however, this is not advised as this may increase the risk of euthanasia when the first episode occurs.

C. In the past, medical treatment of PPID has fallen into **three basic classes of medication:**

1. Cortisol inhibitors (trilostane).
2. Serotonin antagonists (cyproheptadine).
3. Dopamine agonists (pergolide and bromocriptine).

D. The **current recommendation is to use pergolide mesylate** (Prascend®, Boehringer Ingelheim; [1 mg scored tablets]) as **first-line therapy:**

1. Medical treatment of PPID has been used for almost 30 years with early reports in textbooks and review articles originally advocating cyproheptadine, pergolide, or bromocriptine predominantly on a theoretical basis from extrapolation from the human literature.

2. However, based on cumulative evidence, pergolide has become the standard of care recognized in the equine internal medicine literature in horses with PPID.
3. Pergolide (Prascend®, Boehringer Ingelheim) has recently been licensed in some EU countries for use in horses.

E. **Dopamine agonists: Pergolide and Bromocriptine:**
1. The first report of medical treatment of PPID in the scientific literature described a single horse given three dopamine agonists after which the effects of POMC peptides and cortisol were measured.
2. This landmark study demonstrated the benefit of dopamine agonists:
   a. There was inhibition of all the measured POMC peptides (ACTH, β-endorphin, CLIP, α-MSH, and β-MSH) by dopamine infusion, bromocriptine given subcutaneously or orally, and pergolide given orally.
3. Practically, **pergolide mesylate was shown to be the most appropriate dopamine agonist** among the three used. In oral capsule form at a dose rate of 5 mg given once was **well tolerated and effective at lowering POMC peptides** for the duration of the measurement period (48 h):
   a. Dopamine infusion was short acting and produced a rebound increase in POMC peptides following cessation of the infusion.
   b. Bromocriptine was poorly absorbed orally, and while therapeutic levels and an appropriate response were attained, the amount given (100 mg) was much larger per body weight than in man and not well tolerated by the horse. In an attempt to overcome this, subcutaneous injections were used, but these caused local swelling and reactions.
4. Retrospective clinical trial data have shown **pergolide treatment to decrease plasma ACTH concentration and improve clinical signs based on owner reports in as many as 85% of horses with PPID over approximately 2 months of therapy**.
5. Pergolide therapy has been shown in several publications to be **superior to cyproheptadine therapy** and other studies have shown pergolide treatment to be effective after a failed period of cyproheptadine treatment:
   a. When the effects of pergolide and cyproheptadine were compared in a retrospective study of PPID, only two of seven owners reported clinical improvement after treatment using cyproheptadine while 17 of 20 owners reported that pergolide treatment resulted in clinical improvement.
   b. In another study, pergolide was also shown to be a more effective treatment for PPID than cyproheptadine in terms of clinical response (17/20 favorable outcome for pergolide vs 3/7 for cyproheptadine) and normalizing the results of endocrine tests (7/20 vs 1/7, respectively).
6. Pergolide has been associated with **few side effects** where horses start at a dose of 0.002 mg/kg. The most frequently reported side effect is that of **mild inappetence or reduced appetite** and the majority of horses respond to a reduction in dose and then a more gradual increase in dose:
   a. Side effects of inappetence and depression were more commonly reported in earlier studies where initial doses were at the high end of the dose range.
7. The general approach to treatment with pergolide is start at a low dose, increase until clinical signs and endocrine values are well controlled (or signs of intolerance, e.g., inappetence are observed), and then slowly reduce to the lowest effective dose for each horse:
   a. Due to severity and stage of disease and the individual physiological response to therapy, **individual horses may respond differently to treatment.**
   b. **A dose of 0.001–0.002 mg/kg q 24 h**, which represents low dose therapy, is **an appropriate starting dose**.
   c. The dose should be **increased slowly from the starting dose, every 2–4 weeks**, depending on clinical and endocrinological response to **up to 0.01 mg/kg q 24 h**.
   d. Many horses may be able to be maintained on 0.002 mg/kg (low dose), but in the author's opinion, attempting to maintain horses on a lower dose places the horse at risk of treatment failure due to inadequate dose.

F. **Cortisol inhibitors: Trilostane:**
1. Trilostane is a competitive inhibitor of 3-β-hydroxysteroid dehydrogenase.
2. In a 2-year prospective study in 20 horses with PPID, trilostane at 1 mg/kg q 24 h PO was demonstrated to be effective in reducing the clinical signs of PPID, and horses showed a reduction in the cortisol response to TRH 30 days after commencing treatment.

3. Trilostane acts peripherally to reduce clinical signs of disease:
   a. It reduces the effects of hyperadrenocorticism by **inhibiting adrenal cortical glucocorticoid production**.
4. **Clinical signs**, for example, laminitis, muscle catabolism and polyuria/polydipsia and secondary infections **can be reduced**.
5. Trilostane can be considered as an **adjunct therapy** for PPID rather than the main treatment (i.e., pergolide).

G. **Serotonin antagonists: cyproheptadine:**
1. Cyproheptadine has been advocated for the management of PPID in horses on the basis of the fact that high doses of serotonin may stimulate the release of ACTH from the pars intermedia.
2. However, in studies in horses, serotonin stimulation had been shown to have no influence on gene expression of POMC in the pars intermedia.
3. While a marked reduction in dopamine (to <12% of the control value) in PPID affected horses compared with controls has been shown, there was no change in serotonin (5-HT) concentrations between horses with PPID and control horses.
4. Despite the lack of pathophysiological justification, there have been **some reports of clinical benefit from the use of cyproheptadine** and it has been used more recently as an **adjunct therapy in horses responding poorly to pergolide therapy**. The reported dose is 0.25 mg/kg PO q 24 h for 4–8 weeks, increasing to q 12 h dosing at that time if there is a poor response on the basis of clinical signs and repeat laboratory testing.
5. However **the majority of data supports a lack of effect of cyproheptadine** and it has been suggested that any improvement noted with cyproheptadine is due to management adjustments (deworming, dental work, and improved nutrition) rather than the effects of the drug itself.
6. In one study, management adjustments had been performed before the onset of therapy and no effect of cyproheptadine therapy could be detected.

H. **Monitoring:**
1. Once treatment has been initiated, it is important to **continue to monitor the horse clinically as well and endocrinologically**.
2. Horses affected with PPID are aged, and as such **more susceptible to diseases associated with aging** including dental disease, lameness, respiratory disorders and skin disorders.
3. Owners should be encouraged to monitor appetite, hair coat (clip if necessary), water intake and bed wetting when housed, body condition score including estimation of muscle loss as well as fat score, laminitis/lameness, and general demeanor.
4. Horses with PPID will be more susceptible to secondary infections and **regular clinical examinations and hematological and biochemical profiles** are warranted.
5. Monitoring will be quite regular initially as the horse starts treatment.
6. Clinical data as well as **baseline plasma ACTH concentration or dexamethasone suppression test, serum insulin concentration, and blood or urine glucose measurement** can be performed:
   a. The author recommends monthly monitoring initially, with adjustment to the dose of pergolide depending on the response.
   b. Subsequent monitoring can be 3 monthly to 6 monthly, depending on the horse's response.
7. A suggested treatment and monitoring protocol is outlined in Table 11.3.

VII. Prognosis

A. In general, **milder cases respond extremely well to medical therapy** and **treated horses can return to full function**, many cases able to compete in their respective disciplines.

B. **More severe cases** often respond well too, but very advanced cases or those complicated with secondary or concurrent disease, common in aged horses, may not:
1. In such cases, it is important to **utilize endocrinological and clinical variables to determine the response to medical therapy** and formulate a prognosis.
2. The **prognosis is poor if ACTH and insulin remain markedly elevated despite appropriate therapy** at recommended doses.

Table 11.3 Example of a treatment and monitoring protocol for horses with pituitary pars intermedia dysfunction.

This example assumes no concurrent disease and controlled laminitis at the time of treatment. If concurrent disease or uncontrolled laminitis are present, clinical examinations and repeat diagnostic evaluation will necessarily fall within in a shorter time frame.

1. Obtain baseline endocrine and clinical values, for example, basal insulin and glucose, basal adrenocorticotropic hormone (ACTH), and documented clinical examination findings.
2. Owners should be encouraged to monitor appetite, hair coat, water intake and bed wetting when housed, body condition score including estimation of muscle loss as well as fat score, laminitis/lameness, and general demeanor monthly.
3. Calculate the starting dose of pergolide based on 0.002 mg/kg PO q 24 h to the nearest 0.5 mg.

Horse body weight (kg)	Starting daily dose (mg)	Dosage range (μg/kg)
200–350	0.5	1.3–2.5
350–600	1.0	1.7–2.5
601–850	1.5	1.8–2.5

4. After 1 month of once daily treatment, reevaluate baseline endocrine and clinical values as well as owner-reported improvements. You should expect one or more clinical signs to improve and/or the basal ACTH to have returned to normal or close to normal range for that time of year.
5. If clinical and/or endocrine improvements are not noted, increase the dose by 0.001 mg/kg.
6. Reevaluate monthly with increases in the dose by 0.001 mg/kg until clinical signs and endocrinological variables have improved or a maximal dose of 0.01 mg/kg has been reached.
7. If signs of inappetence or depression are observed, reduce the dose by increments of 0.001 mg/kg and investigate for concurrent disease.
8. Once the signs have been successfully controlled, veterinary monitoring can reduce to two to four times per year.
9. Owners should continue to monitor at least monthly and alert their veterinarian if there is deterioration in any clinical sign.
10. If signs are well controlled for >3 months, a slow reduction in the dose by 0.001 mg/kg/month can be attempted, with a minimal dose not less than 0.002 mg/kg.

C. Horses treated with medical therapy earlier, especially prior to the development of laminitis, have the best outcome.

D. Long-term therapy has been shown to be safe and evidence of reduced effectiveness of pergolide over the time frames used for horses (2–7 years) has not been observed.

While affected horses tend to be older, they should not be undervalued or overlooked. Trends in horse ownership are changing and aged horses are more frequently presented for veterinary care. They may be highly experienced athletes or valued by their owners as a companion or teacher.

VIII. Prevention

A. Although there are no specific preventative measures, the importance of early diagnosis and initiation of therapy cannot be overstated.

References and Further Readings

Aleman M, Watson JL, Williams DC, et al. Myopathy in horses with pituitary pars intermedia dysfunction (Cushing's disease). *Neuromuscul Disord* 2006;16(11):737–744.

Beck D. Effective long-term treatment of a suspected pituitary adenoma with bromocriptine mesylate in a pony. *Equine Vet Educ* 1992;4:119–122.

Beech J. Tumors of the pituitary gland (pars intermedia). In: Robinson NE, ed. *Current Therapy in Equine Medicine*. Philadelphia: WB Saunders, 1983, pp. 164–169.
Beech, J. Tumors of the pituitary gland (pars intermedia). In: Robinson NE, ed. *Current Therapy in Equine Medicine 2*. Philadelphia: WB Saunders, 1987, pp. 182–185.
Beech J. Treatment of hypophysial adenomas. *Compendium on Continuing Education for the Practicing Veterinarian* 1994;16:921–923.
Beech J. Diseases of the pituitary gland. In: Colahan PT, Merritt AM, Moore JN, et al., eds. *Equine Medicine and Surgery*, Vol. 2, 5th edn. St Louis: Mosby, 1999, pp. 1951–1967.
Boujon CE, Bestetti GE, Meier HP, et al. Equine pituitary adenoma: A functional and morphological study. *J Comp Pathol* 1993;109(2):163–78.
Cohen ND, Carter GK. Steroid hepatopathy in a horse with glucocorticoid-induced hyperadrenocorticism. *J Am Vet Med Assoc* 1992,200:1682–1684.
Couetil L, Paradis MR, Knoll J. Plasma adrenocorticotropin concentration in healthy horses and in horses with clinical signs of hyperadrenocorticism. *J Vet Int Med* 1996;10(1):1–6.
Donaldson MT, Lamonte BH, Morresey P, et al. Treatment with pergolide or cyproheptadine of pituitary pars intermedia dysfunction (equine Cushing's disease). *J Vet Int Med* 2002;16(6):742–746.
Donaldson MT, McDonnell SM, Schanbacher BJ, et al. Variation in plasma adrenocorticotropic hormone concentration and dexamethasone suppression test results with season, age, and sex in healthy ponies and horses. *J Vet Intern Med* 2005;19(2):217–222.
Dybdal NO, Hargreaves KM, Madigan JE, et al. Diagnostic testing for pituitary pars intermedia dysfunction in horses. *J Am Vet Med Assoc* 1994;204(4):627–632.
Dybdal N, Levy M. Pituitary pars intermedia dysfunction in the horse. Part II: Diagnosis and treatment. In: *Proceedings of the 15th Annual Forum of the American College of Veterinary Internal Medicine*. 1997, pp. 470–472.
Heinrichs M, Baumgärtner W, Capen CC. Immunocytochemical demonstration of proopiomelanocortin-derived peptides in pituitary adenomas of the pars intermedia in horses. *Vet Pathol* 1990;27(6):419–425.
Hillyer MH, Taylor FRG, Mair TS, et al. Diagnosis of hyperadrenocorticism in the horse. *Equine Vet Educ* 1992;4:131–134.
Jørgensen HS. Studies on the neuroendocrine role of serotonin. *Dan Med Bull* 2007;54(4):266–88.
Love S. Equine Cushing's disease. *Br Vet J* 1993;149(2):139–153.
McFarlane D. Advantages and limitations of the equine disease, pituitary pars intermedia dysfunction as a model of spontaneous dopaminergic neurodegenerative disease. *Ageing Res Rev* 2007;6(1):54–63.
McFarlane D, Toribio RE. Pituitary pars intermedia dysfunction (equine Cushing's disease). In: Reed SM, Bayly WM, Sellon DC, eds. *Equine Internal Medicine*, 3rd edn. St Louis: Saunders, 2010, pp. 1262–1270.
McGowan TW. *Aged horse health management and welfare*. PhD Thesis, University of Queensland. 2009.
McGowan CM, Neiger R. Efficacy of trilostane for the treatment of equine Cushing's syndrome. *Equine Vet J* 2003; 35(4):414–418.
McGowan CM, Frost R, Pfeiffer DU, et al. Serum insulin concentration in horses with equine Cushing's syndrome: Prognostic value and response to a cortisol inhibitor. *Equine Vet J* 2004;36(3):295–298.
Miller MA, Pardo ID, Jackson LP, et al. Correlation of pituitary histomorphometry with adrenocorticotrophic hormone response to domperidone administration in the diagnosis of equine pituitary pars intermedia dysfunction. *Vet Pathol* 2008;45(1):26–38.
Millington WR, Dybdal NO, Dawson R, Jr., et al. Equine Cushing's disease: Differential regulation of beta-endorphin processing in tumors of the intermediate pituitary. *Endocrinology* 1988;123(3):1598–1604.
Orth DN, Holscher MA, Wilson MG, et al. Equine Cushing's disease: Plasma immunoreactive proopiolipomelanocortin peptide and cortisol levels basally and in response to diagnostic tests. *Endocrinology* 1982;110(4):1430–1441.
Perkins GA, Lamb S, Erb HN, et al. Plasma adrenocorticotropin (ACTH) concentrations and clinical response in horses treated for equine Cushing's disease with cyproheptadine or pergolide. *Equine Vet J* 2002;34(7):679–685.
Schott HC, Coursen CL, Eberhart SW, et al. The Michigan Cushing's project. In: *Proceedings of the 47th Annual Convention of the American Association of Equine Practitioners*. 2001, pp. 22–24.
Schott HC, 2nd. Pituitary pars intermedia dysfunction: Equine Cushing's disease. *Vet Clin North Am Equine Pract* 2002a;18(2):237–270.
Schott HC, 2nd. Pituitary pars intermedia dysfunction: Equine Cushing's disease. In: Robinson, NE, ed. *Current Therapy in Equine Medicine*, 5th edn. Philadelphia: Saunders, 2002b, pp. 807–811.
Schott HC, 2nd. Pituitary pars intermedia dysfunction: challenges of diagnosis and treatment. In: *52nd Annual Convention of the American Association of Equine Practitioners*. San Antonio, Texas. Ithaca: International Veterinary Information Service (www.ivis.org); Document No. P5308.1206, 2006.
Toribio RE. Pars intermedia dysfunction (equine Cushing's disease). In: Reed SM, Bayly WM, Sellon DC, eds. *Equine Internal Medicine*, 2nd edn. Philadelphia: Saunders, 2004, pp. 1327–1337.
Toribio RE. Adrenal glands. In: Reed SM, Bayly WM, Sellon DC, eds. *Equine Internal Medicine*, 3rd edn. St Louis: Saunders, 2010, pp. 1248–1251.

van der Kolk JH, Ijzer J, Overgaauw PA, et al. Pituitary-independent Cushing's syndrome in a horse. *Equine Vet J* 2001;33(1):110–112.
van der Kolk JH, Kalsbeek HC, van Garderen E, et al. Equine pituitary neoplasia: A clinical report of 21 cases (1990–1992). *Vet Rec* 1993;133(24):594–597.
Wilson MG, Nicholson WE, Holscher MA, et al. Proopiolipomelanocortin peptides in normal pituitary, pituitary tumor, and plasma of normal and Cushing's horses. *Endocrinology* 1982;110(3):941–954.