EQUINE ENDOCRINOLOGY GROUP

Recommendations for the Diagnosis and Treatment of Pituitary Pars Intermedia Dysfunction (PPID)
Revised August 2015

Prepared by the PPID Working Group
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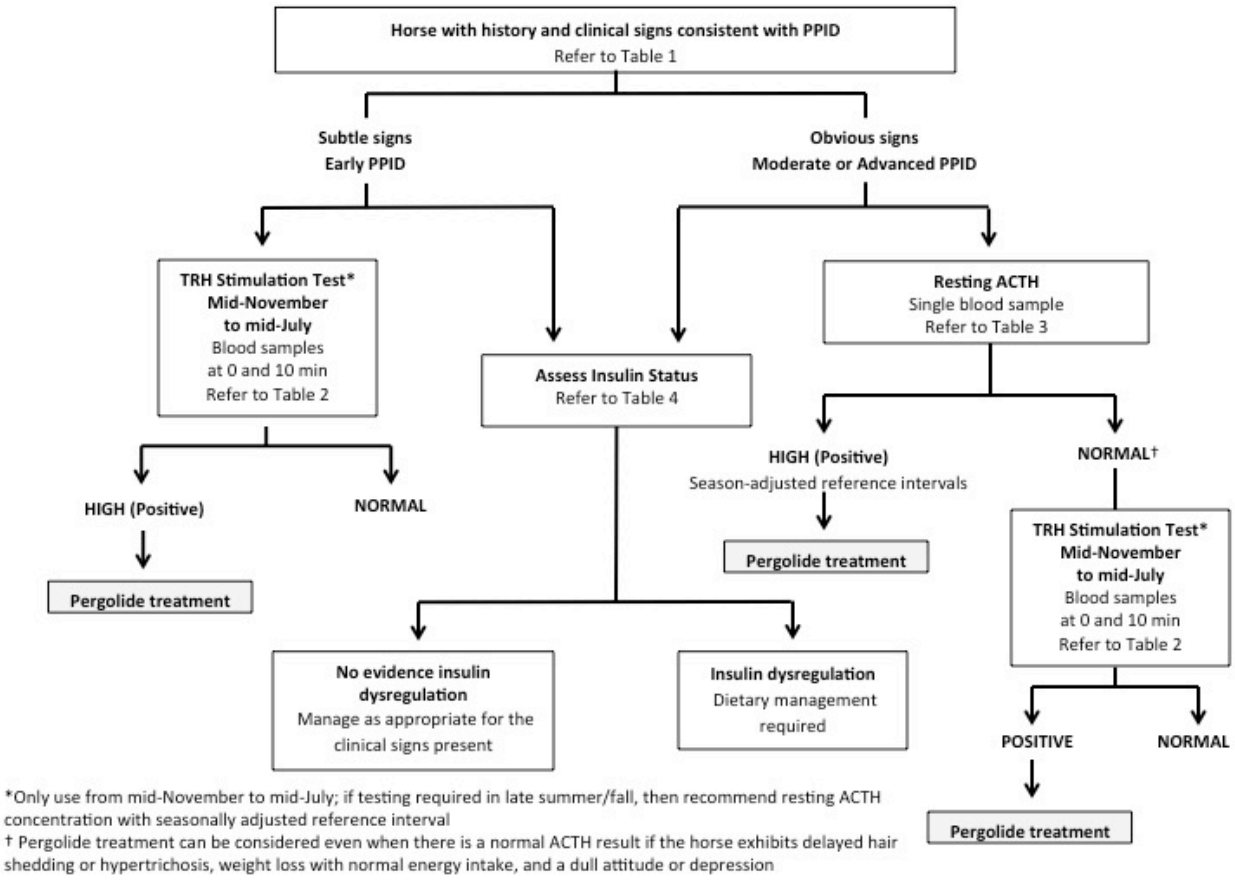

Figure 1 – Algorithm for the diagnosis and management of PPID (August 2015)

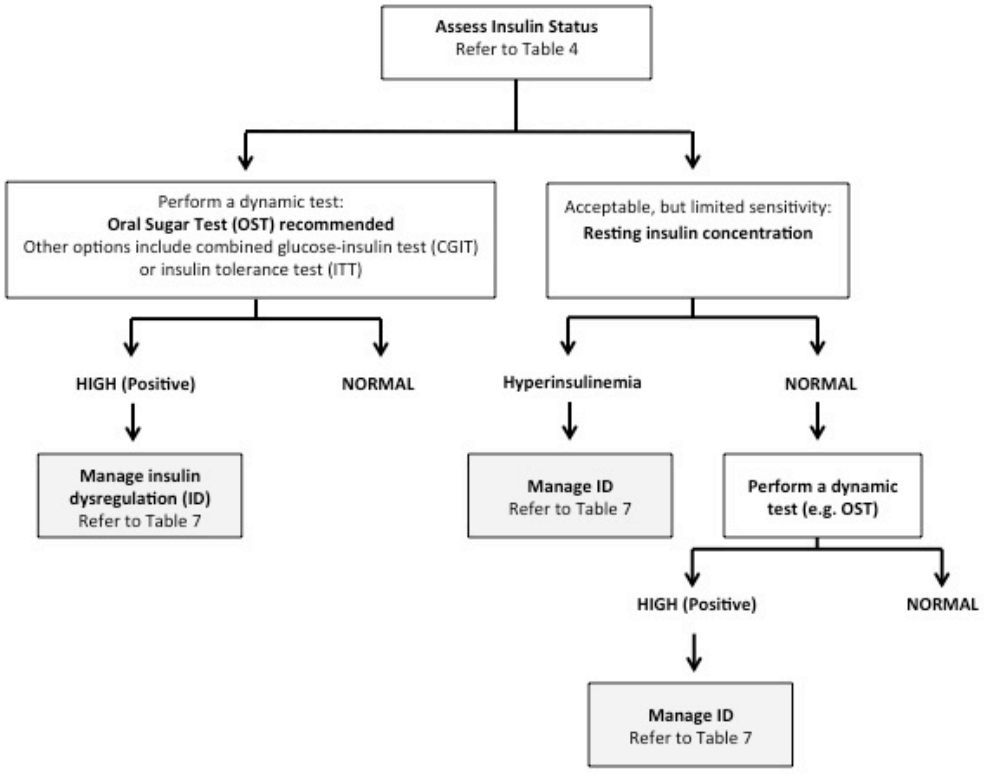

Figure 2 – Algorithm for assessment of insulin status (August 2015)

Table 1–Clinical presentation of pituitary pars intermedia dysfunction

Pituitary Pars Intermedia Dysfunction (PPID) Clinical Presentation	
Early	**Advanced**
Decreased athletic performance	Lethargy
Change in attitude/lethargy	Generalized hypertrichosis
Delayed haircoat shedding	Loss of seasonal haircoat shedding
Regional hypertrichosis	Skeletal muscle atrophy
Loss of epaxial muscle mass (topline)	Rounded abdomen (‘hay belly’)
Regional adiposity	Abnormal sweating (increased or decreased)
Laminitis	Polyuria/polydipsia
	Recurrent infections (e.g. sole abscesses)
	Bulging supraorbital fat
	Absent reproductive cycle / infertility
	Laminitis
	Seizure-like activity
	Blindness
	Parasitism
	Tendon laxity

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Table 2–Thyrotropin-releasing hormone (TRH) stimulation test

<table>
<tr><th colspan="4">Thyrotropin-releasing hormone stimulation test</th></tr>
<tr><td>Procedure</td><td colspan="3">Testing is only recommended from mid-November to mid-July until seasonally–adjusted reference intervals are established.

Horses can be tested under short-term fasting conditions or after hay is fed, but not grain. Do not perform immediately after an oral sugar test.

Veterinarian administers 1.0 mg (total dose) thyrotropin-releasing hormone (TRH) intravenously.

Side effects of TRH are transient and include coughing, Flehmen response, mouthing, and yawning.

Blood samples are collected in tubes containing EDTA at 0 and exactly 10 minutes relative to TRH administration. [a]

Submit plasma for measurement of adrenocorticotropin hormone (ACTH) (process as per table 2)</td></tr>
<tr><td rowspan="5">Interpretation of results</td><td colspan="3">Mid-November to mid-July</td></tr>
<tr><td></td><td>Negative (normal)</td><td>Positive (PPID)</td></tr>
<tr><td>0 min (pre)</td><td>≤ 35 pg/mL[b]</td><td>> 35 pg/mL</td></tr>
<tr><td>10 min</td><td>≤ 110 pg/mL</td><td>> 110 pg/mL</td></tr>
<tr><td colspan="3">Mid-July to mid-November</td></tr>
<tr><td colspan="3">Reference intervals not available at this time</td></tr>
</table>

[a] Sampling at 30 minutes is also acceptable using a cutoff value of 65 pg/mL. This is a higher value than previously recommended (35 pg/mL) and reference intervals for both time points are the subject of ongoing research.

[b]Cornell University Animal Health Diagnostic Laboratory (http://ahdc.vet.cornell.edu/). Consult reference intervals for the laboratory used.

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Table 3–Plasma adrenocorticotropin hormone concentrations

Resting adrenocorticotropin hormone (ACTH) concentration test		
Procedure	Use glass or plastic tubes containing EDTA (purple top) Collect at any time of the day Keep samples cool (ice packs or refrigerator) at all times Centrifuge prior to shipping or freezing Ship via overnight mail with ice packs Preservatives (e.g. aprotinin) or freezing are not required Samples can be frozen, but only after centrifugation (gravity-separated samples will return falsely high results if frozen)	
Interpretation of results[a]	*Use reference intervals provided by the laboratory*	
	Mid-November to mid-July	
	≤ 35 pg/mL	Negative
	Above reference interval	Positive
	Mid-July to mid-November	
	≤ 100 pg/mL[b]	Negative
	Above reference interval	Positive

[a]Note that resting ACTH concentrations are variable, so another sample should be submitted or an dynamic test for PPID performed if the result falls close to the upper limit of reference interval (i.e. equivocal).

Horses with early PPID may fail to demonstrate significant increases in basal ACTH concentrations and retesting between mid-July and mid-November (when test sensitivity is highest) or performing a TRH stimulation test (mid-November to mid-July) is recommended.

[b] There is some evidence that breed of horse affects the magnitude of seasonal increases in ACTH; ponies appear to have greater increases in ACTH in the late summer & autumn.

Table 4–Recommended tests to assess insulin status

Test	Procedure	Interpretation[a]
Oral sugar test Easily performed in the field and more sensitive than the fasting insulin concentration. Recommended as the first choice for assessing insulin status. If the owner has concerns about this test inducing laminitis despite the absence of reported problems, a two-step approach can be followed. First, measure fasting insulin concentrations. If within reference interval, proceed to the OST to further assess insulin status with a dynamic test.	Fasting required (see above) Owner administers 0.15 mL per kg (approximately 75 mL) Karo Light[a] corn syrup orally using 60-mL catheter-tip syringes. Collect blood 60 and 90 minutes after administration of corn syrup. Measure glucose and insulin concentrations.	Normal if the insulin concentration is < 45 µU/mL at 60 and 90 min. Strong support for insulin dysregulation if the insulin concentration is > 60 µU/mL at 60 or 90 min. Weak support for insulin dysregulation if the insulin concentration is 45 to 60 µU/mL at 60 or 90 min. Repeat testing at a later time or consider other tests. Excessive glucose response if glucose concentration > 125 mg/dL at 60 or 90 min.
Resting insulin concentration (glucose also measured) This test is easily performed and can be combined with a resting ACTH measurement. Limitation: Lower sensitivity when compared with the oral sugar test (OST)	For measurement of fasting insulin concentrations, leave only one flake of hay in the stall for 6-12 hours. For measurement of fed insulin concentrations, sample under normal housing & management conditions, but do not feed grain. Collect blood into a tube containing EDTA or serum tube	When fasted, an insulin concentration > 20 µU/mL (mU/L) is supportive of ID. When fed hay, an insulin concentration > 50 µU/mL is supportive of ID. Persistent hyperglycemia indicates diabetes mellitus (insulin is normal or increased) A high insulin concentration is significant, but a normal (low) insulin is not diagnostically meaningful and can be found in normal horses and many with PPID (the oral sugar test is preferred)

[a]Karo Light®; ACH Food Companies, Inc, Cordova, TN. ACTH = Adrenocorticotropic hormone.

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Table 5–Diagnostic tests for pituitary pars intermedia dysfunction (PPID)

Pituitary Pars Intermedia Dysfunction (PPID) **Diagnostic Testing**
Supportive findings Relative neutrophilia and lymphopenia Hyperglycemia Hyperinsulinemia Hypertriglyceridemia High fecal egg count
Recommended tests Subtle signs (early PPID): Thyrotropin-releasing hormone (TRH) stimulation test with ACTH measured* Obvious signs (moderate-advanced PPID): Resting ACTH concentration
No longer recommended Overnight dexamethasone suppression test Oral domperidone challenge test Combined dexamethasone suppression/TRH stimulation test with cortisol measured Magnetic resonance imaging (MRI) specific for pars intermedia enlargement
Not valid for PPID diagnosis ACTH stimulation test Resting cortisol concentration Diurnal cortisol rhythm TRH stimulation test with cortisol measured (without DST) Total cortisol concentration (plasma, urine, or saliva)

* Testing should only be performed from mid-November to mid-July until seasonally–adjusted reference intervals are established

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Table 6 – Treatment plans and monitoring for pituitary pars intermedia dysfunction (PPID)

Treatment of PPID and monitoring	
Initial treatment plan	The FDA-approved pergolide (Prascend; Boehringer Ingelheim Vetmedica, Inc.) is recommended at an initial dosage of 0.5 mg for a 250-kg pony and 1.0 mg for a 500-kg horse (approx. 2 µg/kg) q24h orally. Perform baseline diagnostic testing before starting treatment. The test used to diagnose PPID (e.g., plasma ACTH concentration or TRH stimulation test) can be rechecked as early as 30 days to assess the response to treatment. However, 2 months may be required to fully assess changes in clinical signs. Some horses show a transient reduction in appetite. If this occurs, then stop treatment until appetite returns and then reintroduce gradually by giving partial doses for the first 4 days or by administering half the dose morning and evening.
Initial response (first 30 days)	Improved attitude Increased activity Improvement in polyuria/polydipsia Control of hyperglycemia
Long-term response (1-12 months)	Improvement in haircoat abnormalities Increased skeletal muscle mass Less pronounced rounding of the abdomen Fewer/milder episodes of laminitis Less likely to develop infections
Timeline	The test used to diagnose PPID (e.g. plasma ACTH concentration or TRH stimulation test) should be rechecked after 30 days to assess the response to treatment. A period of 2 months is required before conclusions should be drawn about changes in clinical signs.
Treatment strategies	**Adequate laboratory response with good clinical response of case** If test results are normal at recheck and clinical signs have improved or are stable, the dosage is held constant and the patient is placed on an every six-month recheck schedule, with one appointment occurring in the mid-July to mid-November season. This allows assessment of the patient during the seasonal increase in ACTH concentrations and ensures that treatment is adequate during this period.

	Adequate laboratory response with poor clinical response of case If test results are normal at recheck, but there has been recurrence or development of new problems (i.e, laminitis, bacterial infection, or weight loss), then reassess patient for additional medical problems including insulin dysregulation before assuming that an increase in pergolide dosage is required **Inadequate laboratory response with good clinical response** If test results are abnormal at recheck, yet the patient is responding well clinically, the dosage can be held at the same level or increased, according to the veterinarian's preference. This may be observed more commonly when testing is performed mid-July to mid-November. **Inadequate laboratory response with poor clinical response** If test results remain positive at recheck and the patient is not responding well clinically, increase the dosage by 0.5 to 1.0 mg/day for a 500-kg horse (1-2 µg/kg/day) and recheck after 30 days. Treatment strategies used by the group for refractory cases include gradually increasing the pergolide dosage to 3 mg for a 500-kg horse (6 µg/kg) daily and adding cyproheptadine (0.25 mg/kg PO q12h or 0.5 mg/kg q24h) or gradually increasing the pergolide dosage up to 5 mg for a 500-kg horse (10 µg/kg) daily.

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Table 7 – Other considerations when managing horses with pituitary pars intermedia dysfunction (PPID)

Other Considerations	
Switching horses from compounded pergolide	It may be possible to reduce the dosage of pergolide when switching from compounded pergolide to Prascend. First consider the current status of the horse. If PPID is well controlled, consider a lower dosage of Prascend (maximum recommended reduction of 50%). Retest the horse after 30 days and considering history and physical examination findings to assess response to treatment.
Removing horses from pergolide treatment	In the event that a horse on pergolide treatment misses a dose or is removed from treatment for exhibition/competition, ACTH concentrations may begin to increase within 48 hours, but risk of worsening clinical signs is low for this period.
Quality of life	The majority of horses with PPID are aged and therefore susceptible to non-PPID conditions. Therefore, horse owners should be advised that while medical management of PPID improves quality of life it does not necessarily prolong lifespan.
Wellness care	In addition to medical management, horses with PPID should receive regular wellness care. Special attention should be paid to body condition, dentistry, and parasite control. Adequate water should be available if polyuria/polydipsia are persistent problems. Inadequately controlled PPID horses are at risk for bacterial infections. If insulin dysregulation is also diagnosed, special care should be paid to the horse's diet and access to pasture.
Diet and exercise recommendations	Feed selection should be based upon body condition score and oral sugar test results. Some PPID horses are lean and have normal insulin status, and senior feeds and pasture grazing are appropriate in these cases. Obese (≥ 7/9) horses should be placed on a lower energy diet and exercise program, and those with insulin dysregulation require lower non-structural carbohydrate feeds and limited access to pasture. Feed requirements of aged horses, especially those with PPID, are dynamic and monthly monitoring of body condition score by owners is recommended. Dietary supplements have also been suggested for the management of PPID, but to date, scientific evidence for their efficacy is lacking.