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EVIDENCE REVIEW

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BEVA primary care clinical guidelines: Diagnosis and management of equine pituitary pars intermedia dysfunction

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Abstract

Background: Pituitary pars intermedia dysfunction (PPID) is a prevalent, age-related chronic disorder in equids. Diagnosis of PPID can be challenging because of its broad spectrum of clinical presentations and disparate published diagnostic criteria, and there are limited available treatment options.

Objectives: To develop evidence-based primary care guidelines for the diagnosis and treatment of equine PPID based on the available literature.

Study design: Evidence-based clinical guideline using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.

Methods: Research questions were proposed by a panel of veterinarians and developed into PICO or another structured format. VetSRev and *Veterinary Evidence* were searched for evidence summaries, and systematic searches of the NCBI PubMed and CAB Direct databases were conducted using keyword searches in July 2022 and updated in January 2023. The evidence was evaluated using the GRADE framework.

Results and recommendations: The research questions were categorised into four areas: (A) Case selection for diagnostic testing, pre-test probability and diagnostic test accuracy, (B) interpretation of test results, (C) pharmacological treatments and other treatment/management options and (D) monitoring treated cases. Relevant veterinary publications were identified and assessed using the GRADE criteria. The results were developed into recommendations:

(A) Case selection for diagnostic testing and diagnostic test accuracy: (i) The prevalence of PPID in equids aged ≥15 years is between 21% and 27%; (ii) hypertrichosis or delayed/incomplete hair coat shedding provides a high index of clinical suspicion for PPID; (iii) the combination of clinical signs and age informs the index of clinical suspicion prior to diagnostic testing; (iv) estimated pre-test probability of PPID should be considered in interpretation of diagnostic test results; (v) pre-test probability of PPID is low in equids aged <10 years; (vi) both pre-test probability of disease and season of testing have strong influence on the ability to diagnose PPID using basal adrenocorticotropic hormone (ACTH) or ACTH after thyrotropin-releasing hormone (TRH) stimulation. The overall diagnostic accuracy of basal ACTH

concentrations for diagnosing PPID ranged between 88% and 92% in the autumn and 70% and 86% in the non-autumn, depending on the pre-test probability. Based on a single study, the overall diagnostic accuracy of ACTH concentrations in response to TRH after 30 minutes for diagnosing PPID ranged between 92% and 98% in the autumn and 90% and 94% in the non-autumn, depending on the pre-test probability. Thus, it should be remembered that the risk of a false positive result increases in situations where there is a low pre-test probability, which could mean that treatment is initiated for PPID without checking for a more likely alternative diagnosis. This could compromise horse welfare due to the commencement of lifelong therapy and/or failing to identify and treat an alternative potentially life-threatening condition.

(B) Interpretation of diagnostic tests: (i) There is a significant effect of breed on plasma ACTH concentration, particularly in the autumn with markedly higher ACTH concentrations in some but not all 'thrifty' breeds; (ii) basal and/or post-TRH ACTH concentrations may also be affected by latitude/location, diet/feeding, coat colour, critical illness and trailer transport; (iii) mild pain is unlikely to have a large effect on basal ACTH, but caution may be required for more severe pain; (iv) determining diagnostic thresholds that allow for all possible contributory factors is not practical; therefore, the use of equivocal ranges is supported; (v) dynamic insulin testing and TRH stimulation testing may be combined, but TRH stimulation testing should not immediately follow an oral sugar test; (vi) equids with PPID and hyperinsulinaemia appear to be at higher risk of laminitis, but ACTH is not an independent predictor of laminitis risk.

(C) Pharmacologic treatments and other treatment/management options: (i) Pergolide improves most clinical signs associated with PPID in the majority of affected animals; (ii) Pergolide treatment lowers basal ACTH concentrations and improves the ACTH response to TRH in many animals, but measures of insulin dysregulation (ID) are not altered in most cases; (iii) chasteberry has no effect on ACTH concentrations and there is no benefit to adding chasteberry to pergolide therapy; (iv) combination of cyproheptadine with pergolide is not superior to pergolide alone; (v) there is no evidence that pergolide has adverse cardiac effects in horses; (vi) Pergolide does not affect insulin sensitivity.

(D) Monitoring pergolide-treated cases: (i) Hormone assays provide a crude indication of pituitary control in response to pergolide therapy, however it is unknown whether monitoring of ACTH concentrations and titrating of pergolide doses accordingly is associated with improved endocrinological or clinical outcome; (ii) it is unknown whether monitoring the ACTH response to TRH or clinical signs is associated with an improved outcome; (iii) there is very weak evidence to suggest that increasing pergolide dose in autumn months may be beneficial; (iv) there is little advantage in waiting for more than a month to perform follow-up endocrine testing following initiation of pergolide therapy; there may be merit in performing repeat tests sooner; (v) timing of sampling in relation to pergolide dosing does not confound measurement of ACTH concentration; (vi) there is no evidence that making changes after interpretation of ACTH concentrations measured at certain times of the year is associated with improved outcomes; (vii) evidence is very limited, however, compliance with PPID treatment appears to be poor and it is unclear whether this influences clinical outcome; (viii) evidence is very limited, but horses with clinical signs of PPID are likely to

shed more nematode eggs than horses without clinical signs of PPID; it is unclear whether this results in an increased risk of parasitic disease or whether there is a need for more frequent assessment of faecal worm egg counts.

Main limitations: Limited relevant publications in the veterinary scientific literature.

Conclusions: These findings should be used to inform decision-making in equine primary care practice.

KEYWORDS

ACTH, geriatric, GRADE, horse, insulin, laminitis, pergolide, pituitary, TRH

1 | INTRODUCTION

Pituitary pars intermedia dysfunction (PPID) is a common disease of the older horse and pony.[1] Diagnosis and treatment of the condition can be challenging due to either conflicting literature or a lack of evidence. Most of the literature is expert opinion or case series, and there are only two systematic reviews of the accuracy of one available diagnostic test[2,3] and one systematic review of the efficacy of one treatment[4] to inform clinical decision-making. The development of clinical guidelines is standard practice in human healthcare, and these have been shown to influence clinical decision-making in clinical settings.[5,6] The British Equine Veterinary Association (BEVA) initiated the development of guidelines for clinical practice aimed at equine primary care in an ambulatory setting with topics determined annually by the Editor of *Equine Veterinary Journal* after consultation with the membership and relevant BEVA Committees. Primary care clinical guidelines have been developed for analgesia[7] and wounds[8] in the horse using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework and this study was initiated to develop these for the diagnosis and treatment of PPID.

The aim of this study was to develop evidence-based clinical practice guidelines for the diagnosis and treatment of PPID in the horse. The objectives were to:

1. Identify questions relevant to clinical practice on the diagnosis and treatment of PPID by a panel of first opinion and specialist veterinary surgeons.
2. Appraise the current veterinary evidence for each question through a systematic search of databases and assessment using the GRADE criteria.
3. Make recommendations related to the diagnosis, treatment and monitoring of PPID based on the available evidence.

2 | METHODS

2.1 | Selection of clinical questions

The Editors of *Equine Veterinary Journal* appointed the panel and defined the area for the study as the diagnosis and treatment of equine PPID following the nomination of topics by BEVA Committees for Clinical Practice, Health and Medicine, Ethics and Welfare and Equestrian Sports and consultation with members at their Annual Congress in 2021. Each of the panel members was asked to nominate clinical questions. The panel considered that identifying which animals should be tested for PPID was answerable as a background rather than a clinical question, requiring information on PPID prevalence and clinical presentation to estimate pre-test probability. The remaining clinical questions were then grouped into four categories: diagnostic accuracy of available tests in animals with a low, moderate or high pre-test probability of PPID; interpretation of diagnostic test results; pharmacological agents for medical management of PPID and their side effects, and other treatment/management options; and monitoring pergolide-treated cases. Subsequently, each question category was allocated to two-panel members, who defined PICO elements (population/intervention/comparison/outcome) for each question, with additional definitions for setting and subgroups, as described by GRADE, where relevant.[9] Outcomes of interest were selected based on the expert opinion of the panel, considering their relative importance in clinical practice.[9] The clinical questions for each category are described in Table 1. One additional question that did not fit into this categorisation was considered, namely, are equids with PPID and insulin dysregulation (ID) at increased risk of laminitis compared with equids with PPID without ID? The questions were presented during an online webinar open to all BEVA members for comment.

2.2 | Review of current veterinary evidence summaries

Initial searches for current evidence summaries on equine PPID in the veterinary literature were conducted in the VetSRev database (vetsrev.nottingham.ac.uk) and the *Veterinary Evidence* journal archive (www.veterinaryevidence.org/index.php/ve/search) in August 2022 and January 2023.

2.3 | GRADE review of veterinary publications

2.3.1 | Protocol and registration

The study and the review protocol were not registered. The study methods followed the GRADE handbook[10] where possible.

TABLE 1 Categorisation and listing of clinical questions relating to the diagnosis and treatment of equine pituitary pars intermedia dysfunction following nomination by guidelines panel members.

Category	Clinical questions
Diagnostic test accuracy	What is the accuracy of basal ACTH or ACTH response (10 and 30 min) to TRH administration performed in late summer or autumn for diagnosing PPID in horses with a high/moderate/low pre-test probability (based on signalment and clinical signs) of PPID? What is the accuracy of basal ACTH or ACTH response (10 and 30 min) to TRH administration performed at other times of the year (non-autumn) for diagnosing PPID in horses with a high/moderate/low pre-test probability (based on signalment and clinical signs) of PPID?
Interpretation of diagnostic test results	What is the effect on basal ACTH concentration or ACTH response (10 and 30 min) to TRH administration for diagnosing PPID: • When horses are fed vs. fasted? • In horses with systemic disease? • In obese vs. nonobese horses? • In thrifty vs. unthrifty breeds? • in stressed horses? • In horses with laminitis? • In horses in acute pain? • In debilitated vs. otherwise healthy horses? • In horses resident at different latitudes? • In horses of different coat colour? In horses, what is the effect of repeated TRH administration on ACTH response (10 and 30 min) compared to a single TRH administration for diagnosing PPID? Does concurrent or consecutive dynamic insulin testing affect basal ACTH concentration or ACTH response (10 or 30 min) to TRH administration for diagnosing PPID compared to when performed with no other diagnostic tests?
Pharmacological agents and their side effects, and other treatment/management options	In horses with PPID, does pergolide treatment: • Improve the clinical signs compared to no treatment? • Reduce basal ACTH concentrations or the ACTH response (10 min) to TRH compared to no treatment? In horses with PPID, does compounded pergolide improve the clinical signs or basal ACTH concentrations or the ACTH response to TRH/reduce the side effects compared to pergolide tablets? In infertile broodmares with high ACTH concentrations but without outward signs of PPID, does treatment with pergolide improve fertility compared to no treatment? In late term broodmares with PPID, should pergolide treatment be withheld to reduce the risk of agalactia compared to continuing treatment? In horses with PPID, do alternative therapies such as *Vitex agnus-castus* alone or in combination with pergolide reduce clinical signs or basal ACTH concentrations or the ACTH response (10 and 30 min) to TRH compared to pergolide alone or no treatment? In horses with PPID, does cyproheptadine in combination with pergolide reduce clinical signs or basal ACTH concentrations or the ACTH response (10 and 30 min) to TRH compared to pergolide alone? In horses with PPID, does half dose twice a day administration of pergolide produce fewer side effects and/or a better improvement in the clinical signs or basal ACTH concentrations or the ACTH response to TRH compared to the full dose once daily? In horses with PPID, are there effective treatment options that can be used in pregnancy/lactating horses/horses competing under rules? In horses with PPID, does pergolide have harmful cardiac effects? In horses with PPID whose clinical signs/laboratory tests are stabilised on pergolide, does the dose need to be altered? In horses with PPID and ID, does treatment with pergolide improve insulin sensitivity? In horses with PPID and ID that are treated with pergolide, is improvement in ID associated with improvement in the clinical signs?
Monitoring pergolide-treated cases	In horses with PPID that are treated with pergolide: • Is monitoring of basal ACTH and altering the dose of pergolide accordingly associated with improvement in the clinical signs or basal ACTH concentrations or the ACTH response to TRH? • Is the monitoring of ACTH response (10 and 30 min) to TRH associated with improvement in the clinical signs or basal ACTH concentrations or the ACTH response to TRH?

(Continues)

TABLE 1 (Continued)

Category	Clinical questions
	• Is monitoring of clinical signs associated with improvement in the clinical signs or basal ACTH concentrations or the ACTH response to TRH? • Is seasonal adjustment of pergolide doses associated with improvement in the clinical signs or basal ACTH concentrations or the ACTH response to TRH? • What is the optimal timing post initiation of treatment to assess the endocrine response to treatment? • What is the optimal timing of repeating basal ACTH, ACTH response (10 and 30 min) to TRH or ID testing in relation to pergolide treatment? What time of year is best to assess clinical and endocrine responses? • Does owner compliance influence improvement in the clinical signs or basal ACTH concentrations or the ACTH response to TRH? • Should faecal egg count be performed more regularly than in non-PPID horses? • Should markers of hepatic, renal or any other organ dysfunction be monitored?

Abbreviations: ACTH, adrenocorticotropic hormone; ID, insulin dysregulation; PPID, pituitary pars intermedia dysfunction; TRH, thyrotropin-releasing hormone.

TABLE 2 Inclusion and exclusion criteria used to screen titles and abstracts of publications appropriate for appraisal of evidence on diagnosis and treatment of pituitary pars intermedia dysfunction in the horse.

Inclusion criteria	Exclusion criteria
Original research articles, systematic reviews or structured evidence summaries (including knowledge summaries, BestBETs, CATs)	Single case reports, personal opinion/reviews, textbooks or technical literature
Study published in full, and available in English English language abstracts were assessed, where available, for publications in other languages	Studies not available in English
Published or freely available conference abstracts	
Studies relating to equids including clinical case studies and trials, in vivo and in vitro equine models	

2.3.2 | Eligibility criteria

Limitations on publication date, setting or study population were not imposed (Table 2). Individual case reports were excluded, but no other limitations on study design were imposed. Although not necessarily peer-reviewed, conference proceedings were considered for inclusion if available online, but other grey literature sources were not included.

2.3.3 | Information sources and search

A common strategy for database searches was developed and used as a framework for each individual question. Systematic searches of NCBI PubMed and CAB Direct databases were conducted between April 2022 and August 2022, and updated in January 2023, using common keyword searches with additional search terms added for each clinical question.[11] Abstracts from the Global Equine Endocrinology Symposia that were available online were screened manually for relevant abstracts, and backward citation searching using reference lists of all retrieved publications was undertaken. These guidelines focus on PPID in horses and ponies; therefore, search terms pertaining to donkeys and other equids were not included. However, publications in which donkeys or other equids were included in the study population were not excluded from the review. Specific search terms for each clinical question are described in Tables S1–S7. Records retrieved from each database search were combined, and duplicates were removed.

2.3.4 | Study selection

The title and abstracts of the remaining publications were screened, and those meeting exclusion criteria were excluded at this stage (Table 2). Full-text articles and abstracts were then reviewed to identify relevant publications suitable for evidence appraisal. An unblinded eligibility assessment was carried out independently by panel members. Where abstracts reported findings from the same study as a full publication, only the full publication was assessed to avoid duplication.

2.3.5 | Data collection process

Data were extracted from each publication by each researcher independently using a standard data extraction form. No duplication of data extraction was performed.

2.3.6 | Synthesis of results

GRADE is a transparent framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations; it is the most widely adopted tool for grading the quality of evidence and for making recommendations.[9,12] After deciding what the clinical question is, including the

TABLE 3 Assessment criteria used to alter GRADE quality of evidence.[13]

Reasons to downgrade the evidence quality	Reasons to upgrade the evidence quality
1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	6. Large magnitude of effect 7. Dose response 8. Effect of all plausible confounding factors would be to reduce the effect (where an effect is observed) or suggest a spurious effect (when no effect is observed)
For these five criteria, if • no serious concern exists, do not downgrade quality from the baseline quality (e.g. high for RCTs) • serious concern exists, downgrade the evidence one level, e.g., from high to moderate (−1) • very serious concern exists, downgrade the evidence two levels, e.g., from high to low (−2)	For Criteria 6–8, decide if the evidence should be upgraded once (+1) or twice (+2). Remember RCT evidence quality is very rarely upgraded.

Note: GRADE starts with a baseline rating of high for RCTs, and low for non-RCTs. This baseline rating can then be adjusted (downgraded or less commonly, upgraded) after considering eight assessment criteria and making a judgement about quality based on these.
Abbreviations: GRADE, Grading of Recommendations, Assessment, Development and Evaluation; RCT, randomised controlled trial.

population that the question applies to, and the outcomes that matter most to those faced with the decision, the authors then rate the quality of evidence.[9] GRADE has four levels of evidence—also known as certainty in evidence or quality of evidence: very low, low, moderate and high.[12] Evidence from randomised controlled trials starts at high quality, and evidence that includes observational data starts at low quality.[13] The certainty in the evidence is increased or decreased for several reasons, including risk of bias, imprecision, inconsistency, indirectness and publication bias (Table 3). After assessing the quality of evidence, recommendations are made, which can be strong or weak, in favour of or against an intervention (Table 4).[13] Strong recommendations suggest that all or almost all persons would choose that intervention. Weak recommendations imply that there is likely to be an important variation in the decision that informed persons are likely to make. Recommendations are more likely to be weak rather than strong when the certainty in evidence is low, when there is a close balance between desirable and undesirable consequences, when there is substantial variation or uncertainty in patient values and preferences, and when interventions require considerable resources.[13]

Publications relevant to each clinical question that met inclusion criteria were critically appraised using the GRADE criteria outlined above and summarised. No quantitative quality scoring system was used, and studies were not excluded on quality grounds.

TABLE 4 Factors determining the strength of a GRADE recommendation.[14]

Factor	Comment
Balance between desirable and undesirable effects/ consequences	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

Abbreviation: GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

2.3.7 | Identifying subgroups of the horse at different risk for PPID (pre-test probability)

When making recommendations about the use of diagnostic tests, pre-test probability must be considered.[15] In the absence of any published diagnostic models for PPID or validated clinical decision rules for generating pre-test probabilities, a multi-stage process was used to address the background question regarding case selection for diagnostic testing and to define subgroups of horses based on their pre-test probability. In brief, a list of clinical signs and co-morbidities associated with PPID was collated following the literature review. Together with items regarding horse age, these signs were included in an online questionnaire in the first round of a modified Delphi consultation with panel members.[16] Panel members were asked to indicate the degree to which each sign would prompt them to perform diagnostic testing for PPID, using closed-ended responses on a 7-point interval scale, which ranged from 0 (definitely would not test for PPID) to 100 (definite indication to test for PPID).[16] Consensus for each item was pre-defined as ≥75% of panel members' responses being within a 2-point range, or less, of each other. For items for which consensus was achieved, summary statistics from the first round were provided in the second-round questionnaire and panel members were asked to quantify the degree of clinical suspicion of PPID they would associate with each sign (low, moderate, high or very high). For items where consensus was not achieved in the first round, the questions remained identical. Panel members were provided with a personalised copy of the questionnaire that displayed their initial responses alongside the median and interquartile

range of all first-round responses and were asked to reconsider their choices in light of the panel's response.[16]

Published PPID prevalence estimates and data pertaining to the frequency with which clinical signs were reported amongst veterinary-diagnosed cases and associations between clinical signs and PPID were collated from included publications. Prevalence estimates of PPID in defined populations in the reviewed studies were used to generate estimated values of pre-test probabilities. These values were subsequently used in combination with published sensitivity and specificity estimates to calculate measures of diagnostic accuracy for both basal adrenocorticotropic hormone (ACTH) and ACTH concentration at 10- and 30-min following thyrotropin-releasing hormone (TRH) administration for the diagnosis of PPID, depending on pre-test probability (low, moderate and high).

2.3.8 | Drafting of recommendations

After reviewing the relevant literature and summarising the evidence in pairs, each pair then drafted their recommendations. This was presented at the annual BEVA congress for input from the BEVA membership and two preassigned reviewers appointed by the editors of *Equine Veterinary Journal*. Following this, each pair then drafted their section of the manuscript and circulated it to the remainder of the panel for input. After several iterations, all sections of the final version were approved by all panel members. The article has also undergone *EVJ*'s standard peer review process, except that the usual double anonymous review process was not applied and authors' and reviewers' identities were known to each other.

3 | RESULTS

3.1 | Review of current veterinary evidence summaries

Three systematic reviews[2–4] were identified through searches in VetSRev, all of which met inclusion criteria, and no relevant evidence summaries were identified from *Veterinary Evidence* archive searches.

3.2 | GRADE review of veterinary publications

The total number of relevant studies identified varied between categories and are presented in Tables S1–S7. The summaries and recommendations based on these are presented below.

3.3 | Case selection for diagnostic testing and pre-test probability

One systematic review[17] and 13 additional publications[18–32] were identified that provided data on the frequency of clinical signs within veterinary-diagnosed PPID cases, which were considered in combination with the outcomes from the panel Delphi consultation to categorise clinical signs by the index of clinical suspicion (Table 5). Generalised or regional hypertrichosis (± delayed/abnormal coat shedding) was the most commonly reported sign across all studies (Figures 1–5). Both owner-reported history of hypertrichosis and delayed/abnormal coat shedding have been associated with increased odds of PPID.[1,30] Multiple clinical signs were categorised as providing a moderate index of clinical suspicion for PPID. These signs were

TABLE 5 Summary table of the clinical signs and co-morbidities associated with a high, moderate and low clinical suspicion of equine pituitary pars intermedia dysfunction (PPID).

High clinical suspicion	Moderate clinical suspicion	Low clinical suspicion
Generalised or regional hypertrichosis (M[a])	Hyperhidrosis (M[a])	Inappropriate lactation (VL)
Delayed/incomplete hair coat shedding (L[a])	Abnormal fat distribution/regional adiposity (M)	Corneal ulceration (VL)
	Epaxial muscle atrophy/wasted top line (L[a])	Tachycardia (VL)
	Laminitis (acute and/or chronic) (L[a])	Tachypnoea (VL)
	Weight loss (L[a])	Anhidrosis/heat stress (VL)
	Recurrent/opportunistic infections (L[a])	Exercise intolerance (VL)
	Behavioural changes/lethargy/docility (L[a])	Polyphagia (VL)
	Polyuria and polydipsia (L[a])	Ataxia (VL)
	Pot-bellied appearance (L[a])	Other neurological signs (VL)
	Bulging supraorbital fat (L)	Lightening of coat colour (IE)
	Delayed/poor wound healing (L)	Dull/coarse hair coat (IE)
	Lordosis (VL)	Suspensory ligament degeneration (IE)
	Infertility (VL)	Persistent/recurrent endoparasites (IE)

Note: Letters in parentheses indicate overall GRADE quality of evidence rating, where M = moderate; L = low; VL = very low and IE = insufficient evidence.

[a]Rating was downgraded by one level due to inconsistency in the results, which could not be attributed entirely to differences in PPID case selection between studies.

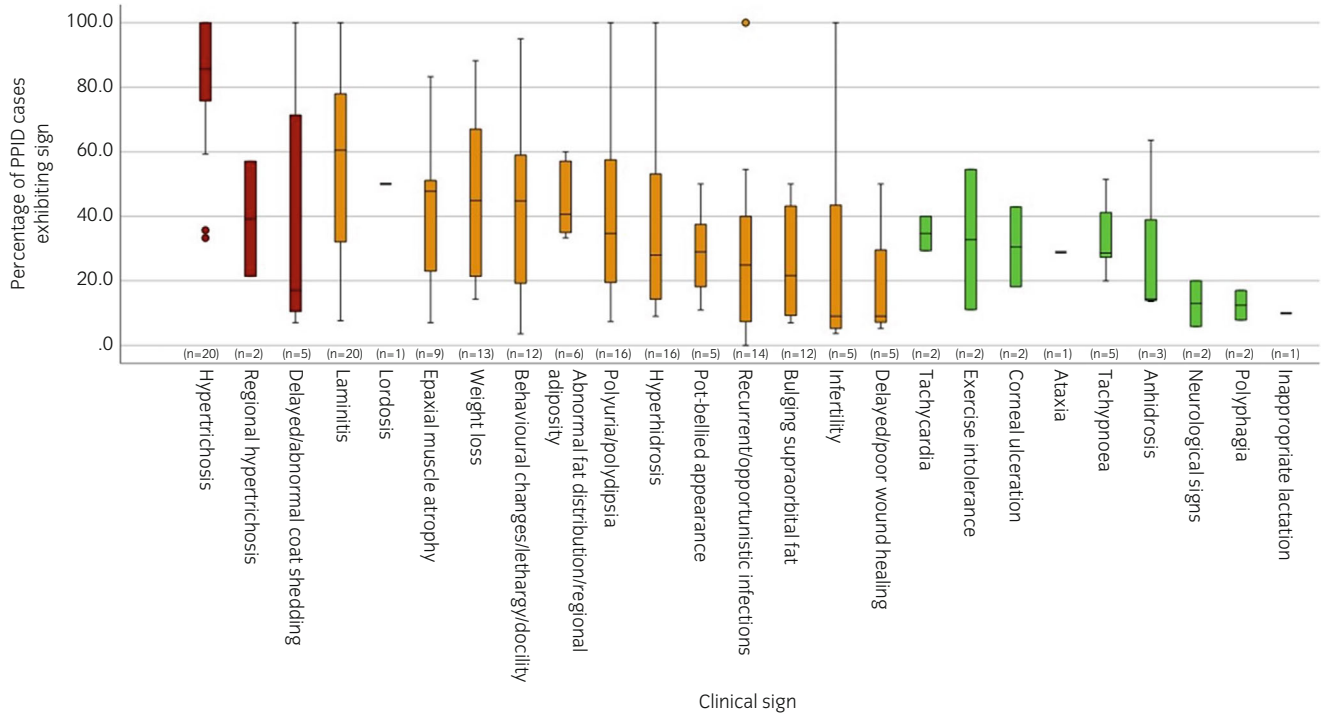

FIGURE 1 Box and whisker plots of the frequencies with which clinical signs and co-morbidities were reported amongst pituitary pars intermedia dysfunction (PPID) cases in included studies, displayed by overall high (red), moderate (orange) and low (green) index of clinical suspicion. Horizontal black lines represent median percentage of PPID cases reported to have each clinical sign, boxes represent interquartile range and whiskers represent full range. The number of included studies providing data on the frequency of each sign amongst PPID cases is reported on the *x*-axis.

reported with variable frequency amongst PPID cases in the literature, and there is no or limited available evidence of a positive association between their occurrence and PPID. Many additional clinical signs were categorised as providing a low index of clinical suspicion for PPID. These signs are reported with variable but low frequency or moderate frequency in a small number of studies amongst PPID cases in the literature, and there is no available evidence of a positive association between their occurrence and PPID. A summary of the key recommendations is presented in Table 6 and Figure 5.

Eleven publications[1,24,28,31,33–39] that provided PPID prevalence estimates in diverse equine populations were identified. For measures of diagnostic test accuracy, the panel chose to make recommendations for equids with a high, moderate, or low pre-test probability of PPID based on the clinical suspicion determined above. The estimate for high pre-test probability was obtained from populations of equids suspected of PPID with veterinary-reported current and/or historical hypertrichosis ± delayed coat shedding. The estimate for moderate pre-test probability was obtained from populations of equids aged ≥15 years, inclusive of any clinical presentation (i.e., average prevalence in aged equids). As no studies that reported PPID prevalence amongst equids presenting only with nonspecific clinical signs were identified, the estimate for low pre-test probability was obtained from veterinary-diagnosed PPID prevalence in the general equine population, irrespective of age or clinical presentation. Using this approach, the high pre-test probability was estimated to be 64%,[1,31,35] the moderate pre-test probability was 24%[24,33] and the low pre-test probability was 3%.[34]

3.4 | Diagnostic test accuracy

Five publications[1,40–43] were identified that provided data on diagnostic test accuracy (Table S3).

3.4.1 | What is the accuracy of basal ACTH performed in the late summer or autumn for diagnosing PPID in horses with a low/moderate/high pre-test probability (based on signalment and clinical signs) of PPID?

Three publications provided seasonally adjusted basal ACTH data collected in the autumn from 242 tests.[1,40,41] The overall sensitivity and specificity of basal ACTH concentrations calculated from these studies were 93% and 88%, respectively. The calculated positive predictive value (PPV), negative predictive value (NPV) and accuracy are shown in Table 7. The calculated numbers of animals that would be

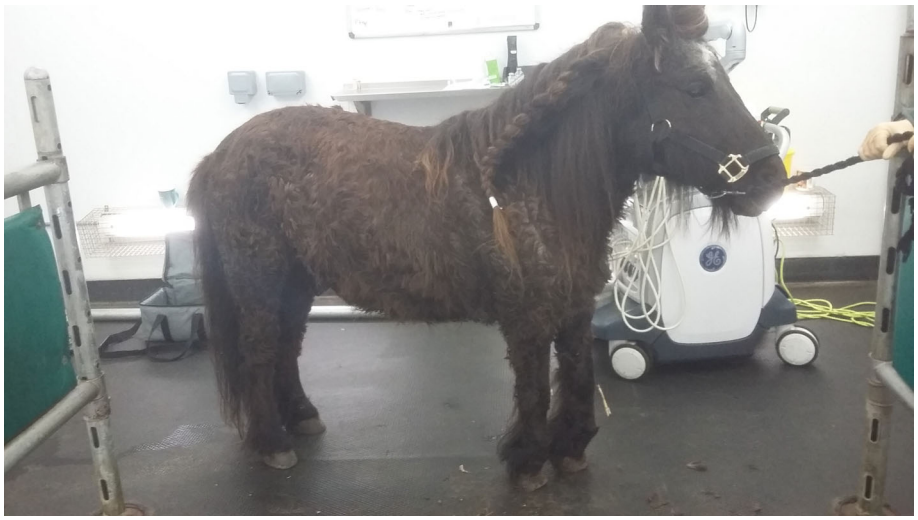

FIGURE 2 Hypertrichosis is the most prevalent clinical sign reported amongst pituitary pars intermedia dysfunction cases in included studies and is therefore considered to have a high index of suspicion.

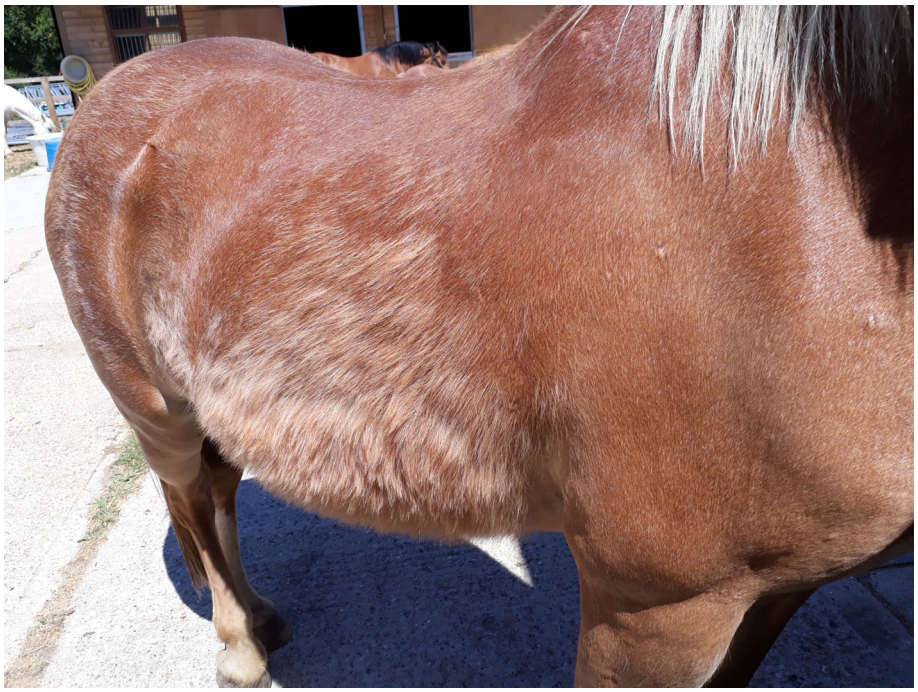

FIGURE 3 Delayed or abnormal coat shedding is a prevalent clinical sign reported amongst pituitary pars intermedia dysfunction cases in included studies and is therefore considered to have a high index of suspicion.

true positive (TP; i.e., are PPID positive and test positive), true negative (TN; i.e., are PPID negative and test negative), false positive (FP; i.e., are PPID negative but test positive) and false negative (FN; i.e., are PPID positive but test negative) in a cohort of 1000 animals tested are shown in Table 8.

In the autumn, a negative ACTH test is strongly suggestive of the absence of PPID, regardless of pre-test probability. In horses with a high pre-test probability of PPID, a positive test in the autumn correctly identifies PPID in ~93% of cases, whereas FP test results occur in ~80% of horses with low pre-test probability and ~40% of horses with moderate pre-test probability. Overall test accuracy ranged from 88% (horses with low pre-test probability) to 92% (high pre-test probability).

3.4.2 | What is the accuracy of basal ACTH performed at other times of the year (non-autumn) for diagnosing PPID in horses with a low/moderate/high pre-test probability (based on signalment and clinical signs) of PPID?

Four publications provided seasonally adjusted, non-autumn basal ACTH data from 1353 tests (Table S3[1,40–42]). The overall sensitivity and specificity of basal ACTH concentrations calculated from these studies were 60% and 87%, respectively. The calculated PPV, NPV and accuracy are shown in Table 7. The calculated numbers of animals that would be TP, TN, FP and FN in a cohort of 1000 animals tested are shown in Table 8.

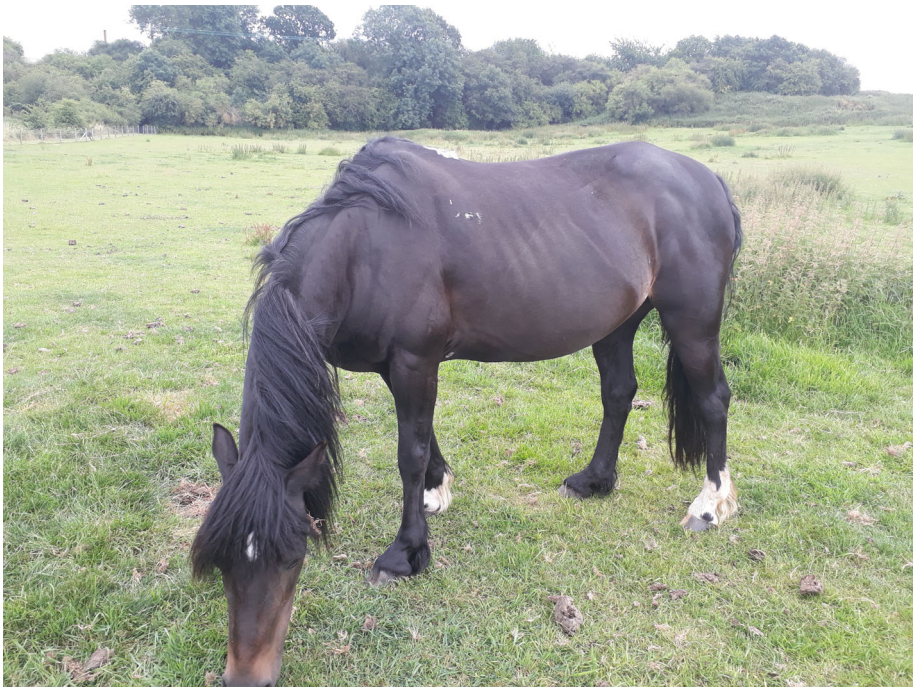

FIGURE 4 Clinical signs which are moderately prevalent amongst pituitary pars intermedia dysfunction (PPID) cases in included studies include weight loss and pot-bellied appearance. Other clinical signs associated with moderate and low prevalence and no or limited available evidence of association with PPID are displayed in Figure 1.

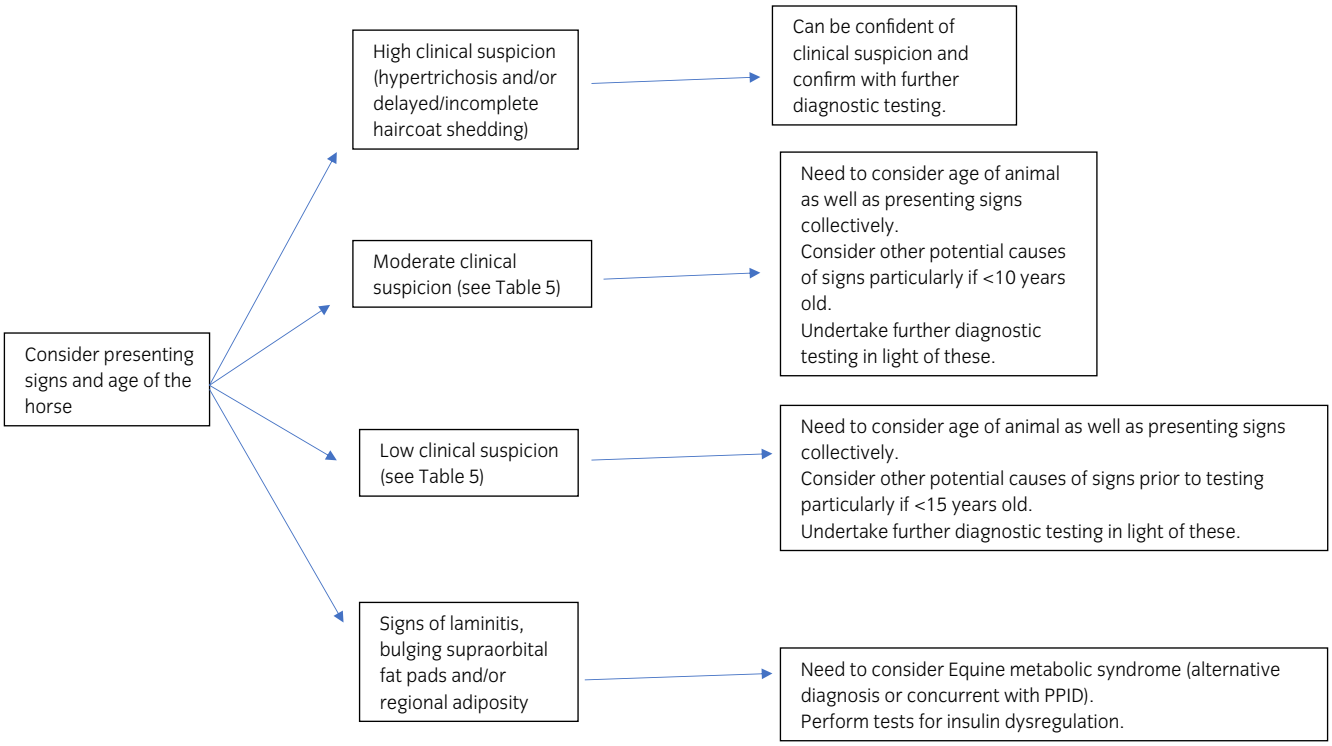

FIGURE 5 Flow chart for interpretation of clinical suspicion.

FP ACTH tests are common in the non-autumn in horses with a low or moderate pre-test probability of PPID. A negative ACTH test in the non-autumn is strong evidence of the absence of PPID in horses with a low to moderate pre-test probability of PPID but less useful in the horse with a high pre-test probability of PPID. Overall test accuracy ranged from 70% in horses with a high pre-test probability of PPID to 86% in horses with a low pre-test probability.

TABLE 6 Summary of key recommendations for case selection for diagnostic testing.

Recommendations for case selection for diagnostic testing	GRADE quality of evidence	GRADE categorisation of recommendation
Clinical diagnosis of PPID is made by a combination of presenting signs and horse age. To facilitate interpretation of diagnostic test results, these should be considered together with expected disease prevalence in comparable populations to estimate pre-test probability for individual cases.	High	Strong
Signs that provide a high index of clinical suspicion for PPID are current and/or historical hypertrichosis or delayed/incomplete hair coat shedding.	Moderate	Strong
For equids of any age exhibiting clinical signs that provide a moderate index of clinical suspicion for PPID, the combination of signs and age should be considered collectively to inform degree of clinical suspicion before diagnostic testing, and other potential causes of clinical signs should be investigated.	Guideline panel consensus	Strong
For equids only exhibiting clinical signs that provide a low index of clinical suspicion for PPID, the combination of signs and age should be considered collectively to inform degree of clinical suspicion. Other potential causes of clinical signs should be investigated, and in equids aged <15 years this would be advisable before diagnostic testing for PPID, given the low pre-test probability in these animals.	Guideline panel consensus	Strong
Pre-test probability of PPID is low in equids aged <10 years. For equids in this age category, other potential causes of clinical signs should be investigated and diagnostic testing for PPID should only be considered in the presence of multiple compatible clinical signs that increase clinical suspicion.	Moderate	Strong
Clinical signs such as laminitis, bulging supraorbital fat and regional adiposity overlap with equine metabolic syndrome, and laboratory testing for insulin dysregulation should be performed in equids presenting with these signs.	Moderate	Strong

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development and Evaluation; PPID, pituitary pars intermedia dysfunction.

3.4.3 | What is the accuracy of ACTH response to TRH after 10 min performed in the late summer or autumn for diagnosing PPID in horses with a low/moderate/high pre-test probability (based on signalment and clinical signs) of PPID?

No suitable publications were identified. Thus, the PPV, NPV and accuracy and the numbers of animals that would be TP, TN, FP and FN in a cohort of 1000 animals tested could not be calculated (Tables 7 and 8) and nothing can be said about the accuracy of ACTH TRH after 10 min (T10) post-TRH.

3.4.4 | What is the accuracy of ACTH response to T10 performed at other times of the year (non-autumn) for diagnosing PPID in horses with a low/moderate/high pre-test probability (based on signalment and clinical signs) of PPID?

Only one study reported ACTH T10 in non-autumn with sensitivity and specificity data.[43] There were also a few studies reporting ACTH post-TRH stimulation at slightly different timepoints or without clearly stating season of testing. The one report included only 12 horses and had a high risk of spectrum bias through case–control design (where horses were selected to have strong clinical signs of PPID or to have no clinical signs). Thus, the PPV, NPV and accuracy and the numbers of animals that would be TP, TN, FP, and FN in a cohort of 1000 animals tested could not be calculated (Tables 7 and 8).

With the current level of literature, nothing can be said about the accuracy of ACTH T10 post-TRH.

3.4.5 | What is the accuracy of ACTH response to TRH after 30 min performed in the late summer or autumn for diagnosing PPID in horses with a low/moderate/high pre-test probability (based on signalment and clinical signs) of PPID?

One publication provided data from 154 tests.[41] The overall sensitivity and specificity of TRH after 30 min (T30) ACTH concentration calculated from this study was 89% and 98%, respectively. However, it should be acknowledged that the same data used to develop the monthly diagnostic cut-off values were used in the calculation of sensitivity and specificity, which can favourably bias the performance calculations.[3] The calculated PPV, NPV and accuracy are shown in Table 7. The calculated numbers of animals that would be TP, TN, FP and FN in a cohort of 1000 animals tested are shown in Table 8.

ACTH response (T30) following TRH stimulation in the autumn is more accurate in horses with low or moderate pre-test probability of PPID and of similar accuracy in horses with high pre-test probability compared to basal ACTH measurement.

3.4.6 | What is the accuracy of ACTH response to T30 performed at other times of the year (non-autumn) for diagnosing PPID in horses with a low/moderate/high pre-test probability (based on signalment and clinical signs) of PPID?

Only one publication provided T30 data collected in the non-autumn with 444 tests.[41] The overall sensitivity and specificity of ACTH response to TRH after 30 minutes calculated from this study was 87% and 94%, respectively. This study used the same population of 104 horses to derive monthly diagnostic cut-off values as used to determine sensitivity and specificity, a practice that can falsely elevate the performance of the test. The calculated PPV, NPV and accuracy are shown in Table 7. The calculated numbers of animals that would be TP, TN, FP and FN in a cohort of 1000 animals tested are shown in Table 8.

ACTH response (T30) following TRH stimulation in the non-autumn is more accurate in horses regardless of their pre-test

TABLE 7 Summary of calculated positive predictive value (PPV), negative predictive value (NPV) and accuracy for basal adrenocorticotropic hormone (ACTH) concentration and the ACTH response to thyrotropin-releasing hormone (TRH) after 10 (T10) and 30 (T30) minutes in autumn and non-autumn in animals with a low, moderate or high (or all animals combined) clinical suspicion of disease.

		PPV (%)		NPV (%)		Accuracy (%)	
Test	Clinical suspicion	Autumn	Non-autumn	Autumn	Non-autumn	Autumn	Non-autumn
Basal ACTH	Low	20	12	99	99	88	86
	Moderate	71	59	98	87	89	80
	High	93	89	88	55	92	70
	All	–	48	–	92	–	–
ACTH response to TRH T10	Low	–	–	–	–	–	–
	Moderate	–	–	–	–	–	–
	High	–	–	–	–	–	–
ACTH response to TRH T30	Low	58	31	100	100	98	94
	Moderate	93	82	97	96	96	92
	High	99	96	83	80	92	90

Abbreviations: ACTH, adrenocorticotropic hormone; TRH, thyrotropin-releasing hormone.

TABLE 8 Summary of the calculated numbers of animals that would be true positive (TP; i.e., are PPID positive and test positive), true negative (TN; i.e., are PPID negative and test negative), false positive (FP; i.e., are PPID negative but test positive) and false negative (FN; i.e., are PPID positive but test negative) in a cohort of 1000 animals tested in autumn and non-autumn using basal ACTH concentrations and the ACTH response to TRH after 30 min (T30).

		Results per 1000 equids tested (95% confidence intervals)							
		Autumn				Non-autumn			
Test	Clinical suspicion	True positive	False positive	True negative	False negative	True positive	False positive	True negative	False negative
Basal ACTH	Low	28 (25–30)	116 (96–136)	854 (834–874)	2 (0–5)	18 (13–23)	126 (105–147)	844 (823–865)	12 (7–17)
	Moderate	223 (215–230)	91 (73–109)	669 (651–687)	17 (9–25)	144 (129–159)	99 (81–117)	661 (643–679)	99 (84–114)
	High	595 (582–608)	43 (31–55)	317 (305–329)	45 (32–58)	384 (359–408)	47 (34–60)	313 (300–326)	256 (231–280)
ACTH response to TRH T10	Low	–	–	–	–	–	–	–	–
	Moderate	–	–	–	–	–	–	–	–
	High	–	–	–	–	–	–	–	–
ACTH response to TRH T30	Low	27 (24–30)	19 (11–27)	951 (943–959)	3 (0–6)	26 (22–30)	58 (44–72)	912 (898–926)	4 (0–8)
	Moderate	214 (205–223)	15 (7–23)	745 (737–753)	26 (17–35)	209 (199–219)	46 (33–59)	714 (701–727)	31(21–42)
	High	570 (554–585)	7 (2–12)	353 (348–358)	70 (55–85)	557 (540–574)	22 (13–31)	338 (329–347)	83 (66–100)

Abbreviations: ACTH, adrenocorticotropic hormone; PPID, pituitary pars intermedia dysfunction; TRH, thyrotropin-releasing hormone.

TABLE 9 Summary of key recommendations for diagnostic test interpretation.

Recommendations for case selection for diagnostic test interpretation	GRADE quality of evidence	GRADE categorisation of recommendation
For repeated sampling of the same individual, it is prudent to test under similar dietary conditions.	Low	Weak
Test for PPID should not be performed in horses that are critically ill.	Moderate	Weak
TRH stimulation tests for PPID should not be performed at intervals shorter than 24 h. At intervals of 2–4 weeks, TRH stimulation are repeatable in non-autumn months but short-term variability in test results during autumn may limit diagnostic accuracy.	Moderate	Strong
Breed may influence basal and post-TRH ACTH concentrations, particularly in autumn. Breed specific reference intervals may be useful.	Moderate	Strong
Basal ACTH concentrations should not be measured immediately after transport.	Moderate	Strong
Pain may affect basal ACTH concentrations and caution should be exercised when considering diagnostic testing for equids in moderate to severe pain.	Low	Weak
Dynamic insulin testing and TRH stimulation testing may be combined but TRH stimulation testing should not follow an OST.	Low	Weak
Geography and latitude affect basal ACTH. Location (rather than just latitude) specific reference intervals may be useful.	Moderate	Strong

Abbreviations: ACTH, adrenocorticotropic hormone; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; OST, oral sugar test; PPID, pituitary pars intermedia dysfunction; TRH, thyrotropin-releasing hormone.

probability of PPID, with a better than 90% accuracy across all groups of horses.

3.5 | Interpretation of test results

In total, 25 publications[41,44–67] and seven abstracts[43,68–73] were identified that provided data on the interpretation of diagnostic test results (Table S4). A summary of the key recommendations is presented in Table 9.

3.5.1 | In horses, how does the fed compared to fasted state affect basal ACTH concentration or ACTH response (10 min) to TRH administration for diagnosing PPID?

Three publications were included.[44–46] Overall, these publications revealed that there may be some effect of diet and/or feeding or withholding feed on basal plasma ACTH concentrations and the effects of withholding feed may also be relevant to TRH stimulation tests. For repeated sampling of the same individual, it is prudent to test under similar dietary conditions.

3.5.2 | In horses, how does systemic disease affect basal ACTH concentration or ACTH response (10 or 30 min) to TRH administration for diagnosing PPID?

Three papers were identified[60,63,66] that suggest basal ACTH concentrations can be increased during illness. Thus, tests for PPID should not be performed in horses that are critically ill.

3.5.3 | In horses, what is the effect of repeated TRH administration on ACTH response (10 and 30 min) compared to a single TRH administration for diagnosing PPID?

Two publications[47,48] and one abstract[43] were included and demonstrated that there was good repeatability of the TRH stimulation test in non-autumn months when performed at intervals of 2–4 weeks; however, during the autumn, more variation should be expected. There was a smaller response of ACTH to TRH stimulation when tests were repeated within 1 day of each other.[45] Thus, TRH simulation tests for PPID should not be performed at intervals shorter than 24 h.

3.5.4 | In horses, how does being obese compared to nonobese affect basal ACTH concentration or ACTH response (10 and 30 min) to TRH administration for diagnosing PPID?

One relevant publication was identified.[41] There were no differences in ACTH concentrations amongst body condition score groups when stratified as low (BCS 1–3), (BCS 4–6) or high (BCS 7–9).[41] Thus, body condition score may not impact testing for PPID.

3.5.5 | In horses, how does being a thrifty compared to an unthrifty breed affect basal ACTH concentration or ACTH response (10 and 30 min) to TRH administration for diagnosing PPID?

In total, four publications[49–51,55] and one abstract[70] were included and revealed that there was a significant effect of breed on basal

ACTH concentration, in particular in the autumn. Some thrifty breeds have higher basal ACTH concentrations than lighter breed horses in the autumn, whilst other thrifty breeds such as Connemara do not. No studies evaluated the effect of breed on post-TRH ACTH concentrations. Thus, breed-specific reference intervals may be useful.

3.5.6 | Does stress affect basal ACTH concentration or ACTH response (10 min) to TRH administration for diagnosing PPID in horses?

Six publications[53,61,62,64,65,68] and one abstract[68] were included. Although there are several papers detailing the impact of exercise on ACTH concentrations, this was not specifically identified as a stressor and so were not included in this review.

Responses to transport by trailer differed between studies, but transport may increase basal ACTH and post-TRH ACTH concentrations.[62,64,65] However, trailer transport was not reported to alter the interpretation of TRH stimulation tests.[68] Novelty stress had a small but significant effect on basal plasma ACTH concentration,[61] while competition stress induced a significant change in basal plasma ACTH concentration that was reduced with increased competition experience.[67] Finally, venepuncture is unlikely to have an effect on most horses.[53] Thus, basal ACTH concentrations should not be measured immediately after transport or acute stress.

3.5.7 | Does laminitis affect basal ACTH concentration or ACTH response (10 and 30 min) to TRH administration for diagnosing PPID in horses?

Two publications[54,60] were included. One revealed that there was no effect of moderate pain on basal ACTH concentrations or the ACTH response to TRH. The second revealed that in horses with laminitis, ACTH concentrations were increased (post-TRH ACTH was not measured) compared to control horses.[60] Thus, mild to moderate laminitis pain may impact basal ACTH or ACTH response to TRH.

3.5.8 | Does acute pain affect basal ACTH concentration or ACTH response (10 min) to TRH administration for diagnosing PPID in horses?

Two publications[54,60] were identified. One[51] indicated that there was no effect of moderate pain on basal ACTH concentrations or the ACTH response to TRH. However, horses with acute abdominal syndrome had higher ACTH concentrations (post-TRH ACTH was not measured) compared to control horses.[60] Thus, mild to moderate pain may impact basal ACTH or ACTH response to TRH.

3.5.9 | Does concurrent or consecutive dynamic insulin testing affect basal ACTH concentration or ACTH response (10 or 30 min) to TRH administration for diagnosing PPID compared to when performed with no other diagnostic tests?

Two relevant publications[45,59] and one abstract[69] were identified. TRH stimulation is lower in horses when administered at 60 min post oral sugar administration in the oral sugar test (OST), compared to being fed or fasted[45]; basal ACTH was not impacted. No clinically relevant difference in TRH-stimulated ACTH (10 or 30 min) was identified when insulin tolerance test (ITT) and TRH stimulation were administered concurrently.[59,69] These findings suggest that basal ACTH may not be impacted by concurrent dynamic insulin testing; post-TRH ACTH concentrations may be impacted by concurrent OST testing; and there appear to be no clinically significant impacts of concurrent testing when using the ITT.

3.5.10 | In horses, how does being debilitated compared to healthy affect basal ACTH concentration or ACTH response (10 min) to TRH administration for diagnosing PPID?

The definition of debilitated use was a state of weakness and loss of ability caused by illness, injury of lack of proper nutrition. No suitable publications were identified.

3.5.11 | What is the effect of different latitude on basal ACTH concentration or ACTH response (10 and 30 min) to TRH administration for diagnosing PPID?

Four publications[51,56–58] and one abstract[73] were included and revealed that whilst latitude impacts ACTH, there are other factors that also play a role in differences identified between locations. Geographic-specific reference intervals should be used rather than just latitude-specific intervals.

3.5.12 | What is the effect of coat colour on basal ACTH concentration or ACTH response (10 min) to TRH administration for diagnosing PPID?

One abstract was identified,[74] which reported that grey horses have higher basal ACTH concentrations than non-grey horses in autumn.

3.6 | Pharmacological treatments and other treatment/management options

In total, one systematic review,[4] 11 publications[20,52,75–83] and two abstracts[22,83] were identified that provided data on the pharmacologic

TABLE 10 Summary of key recommendations for pharmacological treatments and other treatment/management options.

Recommendations for pharmacological treatments and other treatment/management options	GRADE quality of evidence	GRADE categorisation of recommendation
Pergolide improves most clinical signs associated with PPID in most animals except laminitis.	Moderate	Strong
Pergolide treatment lowers basal ACTH concentrations and improves the ACTH response to TRH stimulation in most animals.	Moderate	Strong
Chasteberry may improve some clinical signs of PPID but there is no proven effect on ACTH and there is no benefit to adding chasteberry to pergolide therapy.	Low	Weak
Combination of cyproheptadine with pergolide is not superior to pergolide alone.	Low	Weak
Pergolide does not have harmful cardiac side effects in horses.	Low	Weak
Pergolide therapy does not affect ID.	Moderate	Weak

Abbreviations: ACTH, adrenocorticotropic hormone; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; ID, insulin dysregulation; PPID, pituitary pars intermedia dysfunction; TRH, thyrotropin-releasing hormone.

treatments and other treatment/management options (Table S4). A summary of the key recommendations is presented in Table 10.

3.6.1 | In horses with PPID, does pergolide treatment improve the clinical signs compared to no treatment?

One systematic review was identified,[4] which included 28 publications. Reported improvement in at least one clinical sign following commencement of pergolide treatment ranged from 40% to 100%, with a high proportion of cases (≥76%) showing clinical improvement in most studies. The relative improvement in specific clinical signs following pergolide treatment could be determined in five studies. Improvement in hypertrichosis ranged from 30% to 100%, abnormal fat distribution 0%–33%, hyperhidrosis 15%–45%, lethargy/poor performance 20%–47%, muscle wastage 21%–46% and laminitis 32%–75%, of cases treated with pergolide.[78,81,84,85] One paper published more recently[52] was identified, which reported that pergolide treatment was significantly associated with weight loss and a decrease in hypertrichosis score but had no effect on muscle atrophy score or crest neck score. Thus, pergolide improves most clinical signs associated with PPID in most animals. However, it should be acknowledged that there was only one placebo-controlled study[52] and many of the studies will have been influenced by co-interventions such as management changes and complementary therapies and many of the clinical signs improve with nonspecific treatments.

3.6.2 | In horses with PPID, does pergolide treatment reduce basal ACTH concentrations or the ACTH response (10 min) to TRH compared to no treatment?

One systematic review was identified,[4] which included 28 publications. The proportion of PPID cases demonstrating improvement in plasma ACTH concentrations following pergolide treatment ranged from 20% to 74%. Normalisation of plasma ACTH concentrations to within nonseasonally adjusted reference intervals occurred in 58%–71% of cases,[81,86] while a decrease in plasma ACTH concentrations was reported in 20%–54.8% of cases.[21,78,87,88] One retrospective study reportedly used seasonally adjusted reference intervals when measuring improvement in ACTH concentration following pergolide treatment, in which 28% of cases returned to within these intervals.[87] The same study reported a ≥75% reduction in basal plasma ACTH concentrations in 54.8% of 2122 cases. Another retrospective study using seasonally and geographically adjusted cut-off values reported normalisation of plasma ACTH concentrations in 44.4% of cases overall across multiple repeat tests over a prolonged period.[23] One study reported that ACTH concentration returned to within reference intervals for 74% of cases following pergolide treatment; however, only seasonally adjusted clinical decision limits for initial diagnosis and no reference intervals used for follow-up testing were reported.[83] Two studies reported that ACTH concentration did not significantly decrease in pergolide-treated cases compared to non-treated PPID controls[82] or pre-treatment values[89] over ≥3 months. Conversely, one placebo-controlled trial did report significantly lower plasma ACTH concentrations in pergolide-treated cases over a similar time period.[90] There was some evidence to suggest that a prolonged time period or requirement for an increase in dose (from the median starting dose of 0.002 mg/kg/day) may be needed to achieve a satisfactory endocrine response.[86,87,89,91,92]

Three additional publications were identified which reported that pergolide-treated horses had lower basal ACTH concentrations, but ACTH response to TRH stimulation also improved in the non-autumn,[75] 8 days after initiation of therapy,[76] and improved in 88% of cases and normalised in 24% of cases.[77]

Thus, the available evidence demonstrates that pergolide treatment lowers basal ACTH concentrations and improves the ACTH response to TRH stimulation in most animals.

3.6.3 | In horses with PPID, does compounded pergolide or pergolide paste improves the clinical signs or basal ACTH concentrations or the ACTH response to TRH/reduce the side effects compared to pergolide tablets?

No studies evaluated compounded pergolide; however, one abstract reported that basal ACTH concentrations returned to within the

reference interval in 14 of 19 (74%) cases treated with pergolide paste.[83] Thus, there is limited evidence to suggest that pergolide paste is effective in the treatment of equine PPID; however, the prescribing cascade should be adhered to.

3.6.4 | In infertile broodmares with high ACTH concentrations but without outward signs of PPID, does treatment with pergolide improve fertility compared to no treatment?

No suitable publications were identified.

3.6.5 | In late-term broodmares with PPID, should pergolide treatment be withheld to reduce the risk of agalactia compared to continuing treatment?

No suitable publications were identified.

3.6.6 | In horses with PPID, do alternative therapies such as *Vitex agnus-castus* alone or in combination with pergolide reduce clinical signs or basal ACTH concentrations or the ACTH response (10 min) to TRH compared to pergolide alone or no treatment?

Two publications[20,78] and one abstract[22] were identified. In two studies, the clinical signs consistent with PPID were reported to improve in horses treated with chasteberry (*Vitex agnus-castus*); however, there was no significant difference in the improvement in the clinical signs or basal ACTH between horses treated with pergolide in combination with chasteberry and those treated with pergolide in combination with a placebo. It should also be acknowledged that neither study had an untreated control group, and both comprised small numbers of animals and were reliant on owner assessment of improvement. In the third study,[78] clinical deterioration was observed in 13 of 14 cases treated with *Vitex agnus-castus* and 9 of these animals were subsequently treated with pergolide. Thus, whilst there is conflicting evidence related to the effect of chasteberry on clinical signs of PPID, there is no proven effect on ACTH and there is no benefit to adding chasteberry to pergolide therapy.

3.6.7 | In horses with PPID, does cyproheptadine in combination with pergolide reduce clinical signs or basal ACTH concentrations or the ACTH response (10 min) to TRH compared to pergolide alone?

One relevant publication[19] was identified, which reported that horse owners felt that the response to treatment was greater in horses treated with a combination of pergolide and cyproheptadine (60%), followed by pergolide (40%) or cyproheptadine (29%) alone; although this difference was not statistically significant. Thus, there is no evidence that combination therapy is superior to pergolide alone.

3.6.8 | In horses with PPID, does half-dose twice a day administration of pergolide produce fewer side effects and/or a better improvement in the clinical signs or basal ACTH concentrations or the ACTH response to TRH compared to the full dose once daily?

Whilst some pharmacokinetics studies suggested that the half-life of pergolide is 6–12 h such that twice daily dosing may be more appropriate,[76,93] others suggest that once-daily dosing is likely to be appropriate in most horses with PPID.[89,94] However, there were no relevant studies to address this question and the prescribing cascade should be adhered to.

3.6.9 | In horses with PPID, are there effective treatment options that can be used in pregnancy/lactating horses/horses competing under rules?

No suitable publications were identified.

3.6.10 | In horses with PPID, does pergolide have harmful cardiac effects?

Two relevant publications[79,80] were identified. Treatment with pergolide did not affect the ventricular function, induce valvular disease or affect heart rate in response to exercise. Thus, there is no evidence that pergolide has harmful cardiac side effects in horses.

3.6.11 | In horses with PPID whose clinical signs/laboratory tests are stabilised on pergolide, does the dose need to be altered?

No suitable publications were identified.

3.6.12 | In horses with PPID and ID, does treatment with pergolide improve insulin sensitivity?

Five relevant papers[52,75,81–83] were identified. Most studies failed to identify improvements in insulin concentration in association with pergolide treatment.[75,81–83] However, in an experimental study in which pergolide doses were adjusted monthly based on ACTH concentration over a 12-week period, fasting insulin concentrations were reduced.[52] Thus, the evidence suggests that pergolide does not affect insulin sensitivity.

TABLE 11 Summary of key recommendations for monitoring pergolide-treated cases.

Recommendations for monitoring of pergolide-treated cases	GRADE quality of evidence	GRADE categorisation of recommendation
Continue to monitor basal ACTH concentrations as an objective measure of PPID.	Low	Weak
Monitor clinical signs and adjust treatment accordingly.	Low	Weak
Endocrine responses can be assessed earlier than the 1–3 months that is typically used, to as little as a week or even less.	Moderate	Weak

Abbreviations: ACTH, adrenocorticotropic hormone; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; PPID, pituitary pars intermedia dysfunction.

3.6.13 | In horses with PPID and ID that are treated with pergolide, is improvement in ID associated with improvement in the clinical signs?

No suitable publications were identified.

3.7 | Monitoring pergolide-treated cases

In total, 21 publications[23,75,76,81,84,86,87,89,90,95–105] were identified that provided data on monitoring pergolide-treated cases (Table S6). A summary of the key recommendations is presented in Table 11. An improved outcome was considered as an owner-reported improvement in clinical signs (improved clinical outcome) and/or return of basal ACTH concentration or ACTH response to TRH to within the seasonally adjusted reference range (improved endocrinological outcome).

3.7.1 | In horses with PPID that are treated with pergolide, is the monitoring of basal ACTH and altering the dose of pergolide accordingly associated with an improved outcome?

Six relevant papers[23,75,77,84,86,87,95] were identified. An association between reducing ACTH concentrations and improvement in hypertrichosis or lethargy but not laminitis was identified in a small case series.[84] Monitoring of ACTH concentrations over 5 years or more, and adjusting pergolide doses based on the results, was associated with a clinical improvement in virtually all animals despite endocrine control only being established in around 60% of cases.[85] Assessment of ACTH concentrations and increasing the pergolide doses if suppression is considered inadequate has been associated with good rates of clinical improvement[23,75,95]; however, in the absence of a control population, it is unknown if the act of monitoring ACTH concentration improved outcomes beyond the improvement that would be seen without regular monitoring. In one large laboratory study, increasing the dose of pergolide in response to ACTH results was not associated with an improvement in ACTH concentration at the subsequent ACTH measurement[87]; however, the study was limited by inconsistency in the data and has not been subjected to peer review. It is unclear whether monitoring of ACTH concentrations and titrating of pergolide doses accordingly is associated with improved endocrinological or clinical outcomes, as appropriate studies have not been performed.

3.7.2 | In horses with PPID that are treated with pergolide, is the monitoring of ACTH response (10 and 30 min) to TRH associated with an improved outcome?

Three relevant studies[75,77,87] were identified. Pergolide treatment is associated with a reduction in the ACTH response to TRH in horses with PPID,[75,77,87] but it is unclear whether this is associated with improved endocrinological or clinical outcomes as appropriate studies have not been performed.

3.7.3 | In horses with PPID that are treated with pergolide, is the monitoring of clinical signs associated with an improved outcome?

Six relevant publications[81,84,89,96–98] were identified. Clinical signs can be used as an indicator for response to pergolide therapy,[81,84,96–98] with rates of clinical improvement typically being higher than rates of normalisation of endocrine test results.[89] However, there are no reports that allow the influence of clinical monitoring on prognosis to be determined.

3.7.4 | In horses with PPID that are treated with pergolide, is seasonal adjustment of pergolide doses associated with improved outcomes?

Three relevant publications[75,89,99] were identified. Administration of pergolide to horses with PPID reduces the seasonal rise in ACTH concentration.[75,99] There is no evidence that reducing this seasonal rise, through maintaining or increasing the dose of pergolide, is associated with an improved outcome. However, initiation of therapy at the beginning of autumn did not result in improvement in ACTH concentration or clinical signs until the commencement of winter, which may indicate a need for more aggressive treatment through the autumn.[89]

Thus, the evidence is very weak, but increasing pergolide concentrations in the autumn may be beneficial.

3.7.5 | In horses with PPID that are treated with pergolide, what is the optimal timing post initiation of treatment to assess the endocrine response to treatment?

Five relevant publications[76,84,100–102] were identified. Following the commencement of pergolide treatment, improvement in ACTH concentration is expected within 1 month; all but one of 33 cases improved within 1 month, with the remaining case improving by 3 months.[100] In a small case series, eight of nine horses (88.9%) showed clinical improvement within 14–35 days (average 22.75 days), and seven of those had ongoing improvement for 5–52 weeks (average 21 weeks).[84] Endocrine responses occur in much less than a month; reductions in ACTH, α-melanocyte-stimulating hormone, β-endorphin and corticotropin-like intermediate peptide were reported 48 h following a single dose of pergolide[101] and clinical cases showed a reduction in basal ACTH concentrations within 7 days.[102] In a small experimental study, plasma ACTH concentration reduced significantly within 12 h of pergolide administration, with further reductions occurring up to 10 days after the initiation of treatment[76]; alterations in the response to TRH were identified at 8 days with no further change being identified at 18 days. Thus, there is weak evidence to support the 1- to 3-month follow-up that is typically recommended, and there is evidence that follow-up endocrine testing can be performed much earlier after initiation of treatment.

3.7.6 | In horses with PPID that are treated with pergolide, what is the optimal timing of repeating basal ACTH, ACTH response (10 and 30 min) to TRH or ID testing in relation to pergolide treatment?

Two relevant publications[76,103] were identified. Plasma pergolide concentrations vary fourfold throughout the day in response to once-daily dosing; however, this does not appear to affect ACTH concentration.[76,103] Thus, the timing of ACTH measurement in relation to pergolide administration is unlikely to be clinically relevant.

3.7.7 | In horses with PPID that are treated with pergolide, what time of year is best to assess clinical and endocrine responses?

One relevant publication[89] was identified. When pergolide therapy was initiated in the autumn, ACTH concentrations did not improve substantially until the winter.[89] Assessment of ACTH concentration is typically advocated in spring and autumn, and although this is logical, there is no evidence that it is associated with improved outcomes.

3.7.8 | In horses with PPID that are treated with pergolide, does owner compliance influence outcome?

One relevant publication[104] was identified. In a study of 110 horses on treatment with pergolide, only 48% of horses were receiving ≥90% of the veterinarian's recommended dose of pergolide.[104] Treatment compliance by owners of horses 26 years or older was only 17%, and of Shetland ponies, only 14%; however, control of ACTH concentration was no different between horses belonging to owners that were compliant and noncompliant. Evidence is limited, but owner compliance does not appear to affect basal ACTH concentrations, although it is unclear whether it affects the clinical response to treatment.

3.7.9 | In horses with PPID that are treated with pergolide, should faecal worm egg count be performed more regularly than in non-PPID horses?

Two relevant publications[90,105] were identified. In one study, horses with clinical signs of PPID were found to have higher faecal worm egg count (FWEC) both before and after pergolide treatment when compared with healthy control groups.[105] In another investigation, there was neither a difference in worm egg excretion between horses with sub-clinical PPID and controls nor a difference between pergolide and placebo-treated horses.[90] Evidence is very limited, however, horses with clinical signs of PPID are likely to shed more nematode eggs than horses without clinical signs of PPID. It is unclear whether this results in an increased risk of parasitic disease or whether there is a need for more frequent assessment of FWECs.

3.7.10 | In horses with PPID that are treated with pergolide, should markers of hepatic, renal or any other organ dysfunction be monitored?

No suitable publications were identified.

3.8 | Risk of laminitis in animals with PPID

Nine relevant publications[26,37,102,105–112] and one abstract[113] were identified that were relevant to the risk of laminitis in animals with PPID either with or without concurrent ID (Table S7). These studies revealed that animals with PPID and hyperinsulinaemia appear to be at a higher risk of laminitis than animals with PPID alone. However, any causal association between PPID and ID remains unclear and ACTH and signs of PPID do not appear to be insulin-independent predictors of laminitis risk.

4 | SUMMARY

After considering the background question of identifying which animals should be tested for PPID, evidence summaries were collated

and used to generate recommendations within four broad areas relevant to the diagnosis and treatment of equine PPID.

With respect to case selection for diagnostic testing and diagnostic test accuracy, the prevalence of PPID in equids aged ≥15 years is between 21% and 27%; hypertrichosis or delayed/incomplete hair coat shedding provides a high index of clinical suspicion for PPID; the combination of clinical signs and age informs the index of clinical suspicion prior to diagnostic testing; the estimated pre-test probability of PPID should be considered in the interpretation of diagnostic test results; the pre-test probability of PPID is low in equids aged <10 years; and both pre-test probability of disease and season of testing have strong influence on the ability to diagnose PPID using basal ACTH or ACTH after TRH stimulation. Thus, it should be remembered that the risk of an FP result increases in situations where there is a low pre-test probability, which could mean that treatment is initiated for PPID without checking for a more likely alternative diagnosis. This could compromise horse welfare due to the commencement of lifelong therapy and/or failing to identify and treat an alternative potentially life-threatening condition.

With respect to the interpretation of diagnostic tests, there is a significant effect of breed on plasma ACTH concentration, particularly in the autumn, with markedly higher ACTH concentrations in some but not all 'thrifty' breeds; basal and/or post-TRH ACTH concentrations may also be affected by latitude/ location, diet/feeding, coat colour, critical illness, and trailer transport. Dynamic insulin testing and TRH stimulation testing may be combined, but TRH stimulation testing should not follow an OST. Pain may affect basal ACTH concentrations and caution should be exercised when considering diagnostic testing for equids in moderate to severe pain. Determining diagnostic thresholds that allow for all possible contributory factors is not practical and equivocal ranges are advised. Equids with PPID and hyperinsulinaemia appear to be at higher risk of laminitis, but ACTH and PPID do not appear to be not insulin-independent predictors of laminitis risk.

With respect to pharmacologic treatments and other treatment/management options, pergolide improves most clinical signs associated with PPID in the majority of affected animals; pergolide treatment lowers basal ACTH concentrations and improves the ACTH response to TRH in many animals, but measures of ID are not altered; chasteberry may improve some clinical signs of PPID but there is no effect on ACTH concentrations and no benefit to adding chasteberry to pergolide therapy; combination of cyproheptadine with pergolide is not superior to pergolide alone; and there is no evidence that pergolide has adverse cardiac effects in horses or improves insulin sensitivity.

With respect to monitoring pergolide-treated cases, hormone assays provide a crude indication of pituitary control in response to pergolide therapy; however, it is unknown whether monitoring of ACTH concentrations and titrating of pergolide doses accordingly is associated with improved endocrinological or clinical outcome; it is unknown whether monitoring the ACTH response to TRH or clinical signs is associated with an improved outcome; there is very weak evidence to suggest that increasing pergolide dose in autumn months may be beneficial; there is little advantage in waiting for more than a month to perform follow-up endocrine testing following initiation of pergolide therapy and there may be merit in performing repeat tests sooner; the timing of sampling in relation to pergolide dosing does not confound measurement of ACTH concentration; there is no evidence that measurement of ACTH at certain times of the year is associated with improved outcomes; compliance with PPID treatment appears to be poor and it is unclear whether this influences clinical outcome; horses with clinical signs of PPID are likely to shed more nematode eggs than horses which do not, but it is unclear whether this results in an increased risk of parasitic disease or whether there is a need for more frequent assessment of FWECs.

Most of the recommendations are based on a small number of studies which included small numbers of animals with PPID. This evidence review has highlighted the need for high-quality evidence in the veterinary literature across all areas of the diagnosis and treatment of PPID, and the findings of this study should be incorporated into evidence-based veterinary practice and considered against each individual case to determine the optimal diagnostic tests and treatment.

AUTHOR CONTRIBUTIONS

All authors contributed to the generation of clinical questions, the study design and evidence appraisal. The involvement of each author for each topic is provided in Tables S1–S7. All authors contributed to, reviewed, and approved the final recommendations, and the final paper for submission.

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Nicola Menzies-Gow has previously served as a consultant for and received payments for educational material from Boehringer Ingelheim. Heidi E. Banse has previously served as a consultant for and received research funding from Boehringer Ingelheim Animal Health. Joanne L. Ireland has previously received research funding and payments for CPD material from Boehringer Ingelheim. Edward J. Knowles is employed by CVS UK Ltd and provides clinical diagnostic services through Axiom Veterinary Laboratory. He has received payments from Boehringer Ingelheim for educational material. David Rendle acts as a consultant to companies that perform laboratory testing for PPID and manufacture or distribute treatments for PPID. Other authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICAL ANIMAL RESEARCH

Not applicable.

INFORMED CONSENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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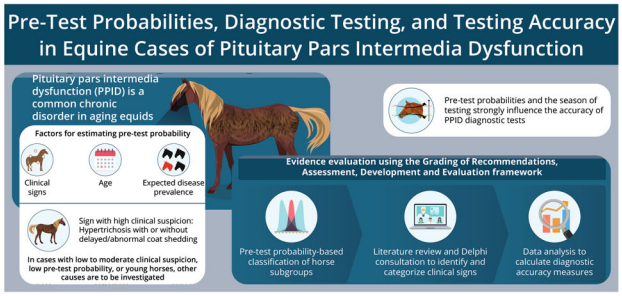
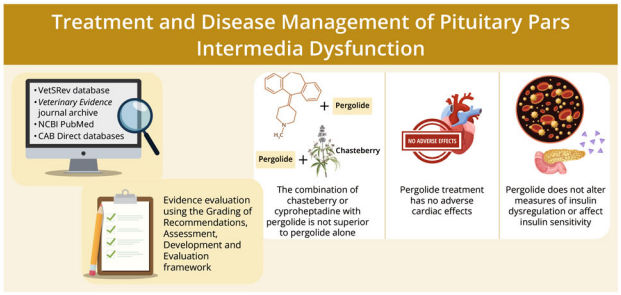
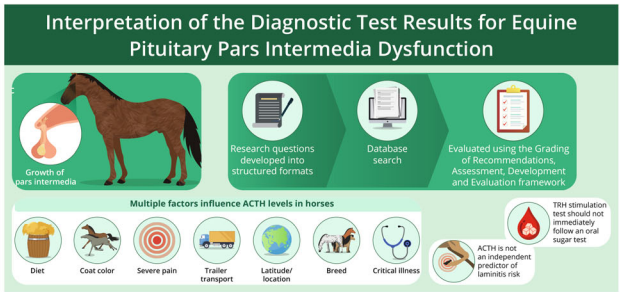
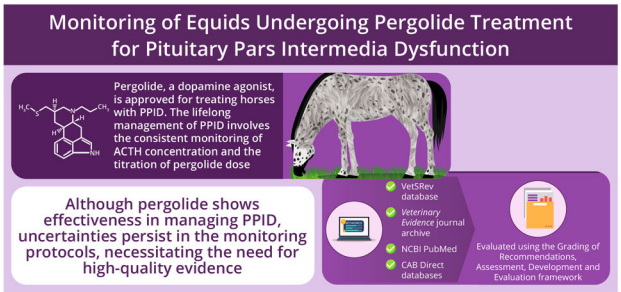
Knowledge Summaries: Key findings from the BEVA Primary Care Guidelines on Diagnosis and Management of PPID

Key findings from this work have been summarised in a series of four infographics which vets can use to remind themselves of the up-to-date information on diagnosis and management of PPID and as simple tools to share with horse owners









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