Effect of endocrinopathies on fertility in the mare Part 2: Pituitary pars intermedia dysfunction

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Abstract

Due to advances in veterinary medicine, equine geriatric population has markedly increased. Without losing perspective of the reproductive problems associated with ageing, it is very important to consider the endocrinologic/metabolic problems (e.g., pituitary pars intermedia dysfunction [PPID; i.e., equine Cushing's disease]) that may also directly impact fertility in this group. PPID is neurological in origin and negatively affects mare's fertility. Frequent clinical signs are: older mare with abnormal, ectopic fat deposits, hirsutism, abnormal estrous cycles, anovulatory follicles, frequent or persistent endometritis, and laminitis. A large number of mares with PPID may develop insulin dysregulation (ID) and insulin resistance (IR) due to the persistent hyperglycemia resulting in ectopic fat deposits or the genetic link that PPID shares with equine metabolic syndrome. Diagnosis of PPID requires a detailed history and physical evaluation combined with appropriate laboratory tests. Treatment for PPID comprises good management and treatment with either dopamine agonists (pergolide, cabergoline) or cyproheptadine, or a combination. A few studies linked or associated subfertility with this condition, and clearly, there is a need for further investigation.

Keywords: Age, insulin dysregulation, mare, fertility, hirsutism

Introduction

Equine Cushing's disease, or pituitary pars intermedia dysfunction (PPID), is an endocrinologic/metabolic abnormality observed mainly in geriatric horses.[1,2] Although all breeds can be affected, it is more prevalent in ponies and Morgans. It is characterized by excessive secretion of adrenocorticotropin (ACTH) and other peptides. In normal horses, almost all circulating ACTH comes from the pars distalis and only a minimal amount comes from the pars intermedia. In the latter case, the primary peptides produced are α-melanocyte stimulating hormone (α-MSH), ß-lipotropin (βLPH), ß-endorphins and corticotropin-like intermediate peptide (CLIP) that are all associated with energy balance and metabolism.[3] This condition appears to negatively affect mare's fertility and should be suspected when observing the following clinical signs: older mare (i.e., ≥15 years of age), with abnormal, ectopic fat deposits that have not completely lost winter hair, or do it later than normal, abnormal estrous cycles, anovulatory follicles, frequent or persistent endometritis, and laminitis. Age is the primary risk factor and the clinical signs progress slowly making early diagnosis difficult.[4]

Pituitary pars intermedia dysfunction

Pathophysiology

Pituitary pars intermedia dysfunction is a neurodegenerative disease with loss of the inhibitory dopaminergic input to the melanotrophs of the pars intermedia.[1-4] The cause is unknown; however, oxidative stress is suspected. Activity of the equine pars intermedia is stimulated by thyrotropin-releasing hormone (TRH) and possibly serotonin. It is inhibited by dopamine secretion. The endocrine cells of the pars intermedia, the melanotrophs, receive direct innervation from the dopaminergic neurons of the hypothalamic periventricular nucleus.[4] If dopamine is low or absent, melanotropes will proliferate and undergo hypertrophy resulting in an increase production of proopiomelanocortin (POMC)-derived peptides.[5] Activity of the par intermedia is influenced by a seasonal, circannual rhythm which causes high hormonal production as daylength shortens.[4,6] This results in an increased secretion of POMC-derived peptides that stimulate an increase in appetite and adipogenesis in preparation for feed shortage in winter.

Chronic exposure to elevated concentrations of these hormones results in several clinical signs. The most common findings are hirsutism or changes in haircoat, weight loss

caused by muscle atrophy, lethargy, secondary infections, and laminitis. Most likely laminitis occurs only in horses with concurrent insulin dysregulation (ID).[4] Affected horses may exhibit neurologic disturbances occasionally.[7]

Effects of PPID on reproduction in the mare vary due to confounding factors such as age, presence of PPID alone or with ID, obesity and/or ID. Frequent clinical signs of PPID in reproduction are ovarian inactivity, cycle aberrations or absence, anovulatory follicles and endometritis. A high percentage of mares experience galactorrhea due to hyperprolactinemia.

Possible systemic and local mechanisms of action of persistent high ACTH, other pars intermedia peptides and glucocorticoids on reproduction in the mare

Limited information is known about the reproductive hormonal environment in mares with PPID and the consequences for fertility. PPID is observed in mares > 15 years old (already have an age-related decline in fertility). Mares older than14 years take longer to conceive than younger mares. They also have lower live foal rates (>13 years) and higher early embryonic death (EED) and abortion rates (> 8 years).[8,9] Increasing age in mares predisposes them to PPID. Therefore, suspecting and testing for this disease should be warranted when presented with old mares for reproductive management.

To understand seasonality, few studies were able to mimic a 'transient PPID' by treating normal mares during seasonal anestrus with dopamine antagonists (e.g., sulpiride or domperidone).[10,11] In treated mares, advancement of first seasonal ovulation, prolactin secretion, and higher concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH) were observed at first ovulation.[10] Also, inhibition of the dopaminergic neurotransmission resulted in increased follicular development and estrogen and prolactin secretion.[11] In conclusion, dopamine appears to have a role in the control of reproductive seasonality and produces a tonic inhibition of the reproductive activity during seasonal anestrus. These findings may also explain why some of the mares keep cycling during winter (without obesity or ID). It will be critical to adjust the dose of pergolide when treating a PPID mare since it could affect her cyclicity and reproductive performance.

Persistently higher concentrations of ACTH may result in a chronic increase of glucocorticoids and sex steroids in the mare. Adrenocorticotropic hormone treatment to intact mares increased blood concentrations of cortisol, progesterone, androstenedione, and testosterone, suggesting crosstalk between the hypothalamic-pituitary-adrenal (HPA) axis and the reproductive system. Authors speculated that the adrenal gland, and not the ovary, was the most likely source of these hormones, since similar results were obtained in ovariectomized mares.[12] Higher concentrations of testosterone, estrogens, or progesterone inhibit gonadotropin releasing hormone (GnRH) release from the hypothalamus and negatively affect LH release. Increased concentrations of glucocorticoids or hypercortisolemia are inconsistent in the mare with PPID, but if present, they may also negatively affect fertility. Hypercortisolemia has been evaluated in stressful situations (e.g., transportation and artificial insemination) in the mare without finding a detrimental effect. However, it has not been thoroughly evaluated in mares with PPID.[13]

Although studies mainly concentrated on effects of high and persistent concentrations of ACTH and cortisol over the HPA axis and the ovaries, some other peptides involved in PPID may be responsible for the impaired reproductive function. For example, ß-endorphins inhibit LH release and stimulate prolactin release. Although prolactin is secreted from the pars distalis and not the pars intermedia, it is usually elevated in mares with PPID. This is because prolactin secretion is also controlled by dopamine from hypothalamic neurons that are damaged in PPID. Dopamine that regulates lactotrophs is delivered via the portal blood system whereas dopamine that regulates melanotrophs is delivered via neural input. In humans, high concentrations of prolactin inhibit GnRH release and the same could be true for the mare. Finally, it has been postulated that pars intermedia adenomas may expand and compress the pars distalis and hypothalamus resulting in loss of function (inhibition of FSH and LH release).[14]

There are a few reports concerning ACTH and cortisol concentrations during estrous cycle and pregnancy in normal mares. ACTH, but not cortisol, insulin, or glucose concentrations, increased during the periovulatory period and during early pregnancy in normal mares.[15] Unfortunately, they did not measure androgens, estrogens, or progesterone concentrations to evaluate if the increased ACTH had some direct or indirect effect on ovarian steroidogenesis. Authors emphasized that the increased ACTH concentrations during the periovulatory period and pregnancy are mild and unlikely to be clinically relevant for early diagnosis of PPID. However, they suggested that an increase in the dose of pergolide may be warranted in early pregnancy.

Concentrations of ACTH and cortisol increased at ovulation (as evident by frequent sampling) in Spanish Purebred mares that reinforced the role of the HPA axis in the mare's ovulatory mechanism.[16] These hormones had similar biphasic patterns; the first highest hormonal peak occurred on the day of ovulation and the second on day +5, indicating some degree of participation of the HPA axis in follicular development, ovulation, and CL formation. Increased and sustained concentrations of ACTH and/or cortisol, as occurs in PPID, may alter this mechanism.

Cortisol concentrations increased in mares with higher (> 100 pg/ml) and intermediate (50 - 100 pg/ml) ACTH concentrations compared to mares with lower ACTH concentrations (< 50 mg/ml).[17] Fertility, measured by conception and foaling rates, was significantly lower in the group with higher ACTH concentrations. Authors speculated that mares with higher ACTH concentrations may have had hypercortisolemia that predisposed them to uterine infections, resulting in lower conception rates. However, there were no significant differences in age; ovarian or uterine status; and uterine cytology or biopsy findings among groups. There was a higher percentage of mares in the high ACTH group with vaginal and cervical lesions, and it was suggested that this was probably associated with higher number of matings needed and dystocia or problems from previous deliveries. However, there was no significant difference among groups in the number of matings .[17]

Possible effect of elevated glucocorticoids

In humans, higher cortisol concentrations have an inhibitory effect on GnRH release from the hypothalamus. This decline in GnRH secretion reduces the secretion of FSH and LH from the pituitary gland, disrupting folliculogenesis and ovulation.

Another mechanism of hypercortisolemia in humans appears to be direct suppression of the pituitary response to GnRH lowering gonadotrophin release, especially LH secretion. In rats, there is a differential response to glucocorticoids from pituitary cells: secretion of LH is decreased and FSH secretion is increased. These alterations will indirectly affect ovarian steroidogenesis, follicular development, ovulation, and oocyte quality.[18] Furthermore, glucocorticoids can also affect ovulation by acting locally at the level of ovaries. Direct effect of glucocorticoids on the ovary depends on binding to its receptor (GR) that in humans is present in follicles, CL, and ovarian epithelium. Higher concentrations of cortisol in follicular fluid negatively influence oocyte maturation and fertilization in women undergoing in vitro fertilization.[19] Similar mechanisms may exist in mares with PPID that have anovulatory follicles, ovarian inactivity, or atrophy, but further studies are needed.

In mares, stress due to transportation, gynecological manipulation, artificial insemination, pregnancy, nutritional imbalance, exercise, pain, and social stress, induces an increase of ACTH and cortisol that may negatively affect fertility.[16] Mares treated with dexamethasone (a synthetic glucocorticoid) at 30 mg/day for 10 days had a significant reduction in LH concentrations and follicular size.[20] Ovulation occurred in 1 and possibly in 2 of 8 treated mares, compared to all 8 control mares.[20]

Prolonged treatment of mares with dexamethasone (0.05 mg/kg twice daily for 5 days) suppressed endogenous cortisol concentrations, resulted in lower uterine edema scores at 24 hours and a reduced ovulation rate compared to placebo-treated mares (40 versus100%, respectively).[21] Three of the 5 dexamethasone-treated mares did not have an LH surge that ultimately affected ovulation.[21] Results demonstrated that dexamethasone could interfere with ovulation and associated events in the mare. However, whether this information can be extrapolated to mares with PPID is still unclear.

It has been suggested that higher concentrations of glucocorticoids, through its immunosuppressive effects, can predispose mares with PPID to infectious endometritis. Nevertheless, compounding factors (e.g., poor perineal conformation, tight cervix, and a pendulous uterus) may also have a role since this is usually an older group of mares.

Pituitary pars intermedia dysfunction and insulin dysfunction associated disease

This is a frequent scenario due to the persistent hyperglycemia and consequent fat formation and deposit but, especially, due to the possible genetic link between these two diseases.[22] Both conditions should be treated individually since correcting the ACTH concentrations with dopamine agonists treatment will not correct the ID.[23] Therefore, it is advisable to have pharmacological treatment for PPID and at the same time, manage the EMS component with diet and exercise.

Diagnosis

Affected horses are generally older (≥ 15 years) with hirsutism and the above-described clinical signs. Some of the clinical signs are associated with normal ageing or with the concurrence of EMS. The presence of hirsutism has more diagnostic power than any endocrine test alone or combined.[3] There are dynamic, static, and combined endocrinological tests.

Static tests

Baseline ACTH concentrations: It is used for moderate to severe_cases with obvious clinical signs. Values < 35 pg/ml are considered normal from November to July and < 100 pg/ml from August to October.[3,14,24]

Fasting serum insulin concentration

Although insulin and glucose concentrations are not diagnostic of PPID, this test is highly recommended since 25 - 75% of horses with PPID also have insulin resistance. Baseline insulin values > 20 µu/ml are indicative of ID and values > 30 µu/ml are considered diagnostic

Dynamic tests

Dexamethasone suppression test: This test is for moderate to severe cases. Currently, it is not recommended as first-line testing for PPID.[24]

When normal ACTH concentrations are accompanied by clinical/subclinical signs of PPID, it is recommended to perform the thyrotropin releasing hormone (TRH) stimulation test by measuring responses in ACTH cocentrations.[24,25]

Diurnal Cortisol Rhythm: This test is no longer recommended. However, it may be useful for practitioners with limited access to laboratories that measure ACTH concentrations

In summary, the recommended tests based on the stage of the disease are the following: when subtle signs (early PPID), use TRH stimulation test with ACTH measurement or resting ACTH concentrations. When obvious signs (moderate to advanced) use resting ACTH concentrations.

Horses that exhibit early subclinical signs of PPID ('precushingoid') with normal laboratory results should be reevaluated every 4 - 6 months, avoiding the fall.

Treatment

Management of horses with PPID includes pharmacological treatment and good management practices. The latter should include frequent body clipping, care of hooves and teeth, adequate nutrition, and the use of antibiotics when necessary. The drug of choice is the oral dopamine agonist pergolide mesylate at 1 - 5 mg/day/500 kg. In pregnant and lactating animals, pergolide may increase the risk of prolonged preg-

nancy, premature placental separation, and hypo-agalactia, as it will mimic fescue toxicity in a pregnant mare.[8,26] Treatment with pergolide should be discontinued in pregnant mares 30 days before expected due date to avoid these adverse effects. Dopamine antagonist treatment (e.g., domperidone or sulpiride) should be considered if the mammary gland does not develop at the expected rate.[8,27,28] However, the use of domperidone to support lactation whereas treating with pergolide has been ineffective.[8] Pergolide treatment should be reinitiated by 30 days postpartum.

Another dopamine agonist drug that is recommended for the treatment of PPID is cabergoline in a slow-release vehicle (Cabergoline 5 mg/ml BET Pharmacy, Lexington, Ky) at 2.5 - 5 mg/500 kg/every 10 - 14 days. Cabergoline did not correct insulin dysregulation in mares with PPID and EMS associated disease.[23] Another drug used alone or in combination with pergolide is a serotonin antagonist, oral cyproheptadine at 0.25 mg/kg/ every 12 or 24 hours or 200 - 400 mg/500 kg every 24 hours. Implementation of this therapy is based on the effect of serotonin on ACTH secretion by the pituitary gland as in rats.[3,29] Its use alone is controversial since the results (28% improvement) are comparable to those obtained with only good management.[30]

Conclusion

PPIS and EMS have been associated with subfertility in the mare, probably through their effect on the estrous cycle and ovarian follicular dynamics. However, confounding factors are age and insulin dysregulation. It is important to make an accurate diagnosis since treatment on 'a trial-and-error basis' is not without adverse consequences. The use of appropriate laboratory tests in conjunction with clinical signs is paramount in the diagnosis and management of this condition.

Conflict of interest

None to declare.

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