Reproductive effects of equine endocrine disease

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Abstract

Endocrine disease is very common in domestic horses and ponies and has become even more so as members of these populations are currently living relatively longer. Older animals are now often successfully fulfilling their intended use (competition, pleasure riding and reproduction) well into their third decade. Therefore, managing influence of endocrine diseases (many of which increase in frequency with age) on fertility and reproductive outcomes will likely be more important for veterinary practitioners in the future. Relatively little is known about specific effects of equine metabolic syndrome and pituitary pars intermedia dysfunction on reproductive function in horses, although preliminary information describing some effects on fertility, ovulation efficiency, implantation, duration of pregnancy and lactation have been published. Further work characterizing these influences will ideally lead to establishment of concrete guidelines and best practices to optimally manage older breeding animals affected by endocrine disease.

Keywords: Equine metabolic syndrome, pituitary pars intermedia dysfunction, insulin dysregulation, pregnancy

Hormonal effects of obesity and insulin dysregulation on equine reproductive function

Horses with equine metabolic syndrome (EMS) by definition have insulin dysregulation (ID) and are frequently persistently hyperinsulinemic.[1] Mares with EMS are suspected to have altered reproductive physiology, with some investigators correlating elevated serum insulin concentrations and poor fertility. Body condition score and percentage body fat were reported to be inversely correlated to systemic insulin sensitivity and directly (positively) correlated to blood expression levels of IL1 and TNFα in mares;[2] these changes were more prominent in older animals, suggesting a relationship between age-related systemic insulin resistance (IR) and age-related decline in fertility in mares. When systemic IR was experimentally induced in mares with a heparin and lipid infusion, an increased interovulatory period and higher peak luteal progesterone concentrations resulted.[3] Insulin has also been evaluated as a potential candidate for the signal for equine maternal recognition of pregnancy (MRP); however, after observing that 1) insulin administration did not affect luteal size, diestrus length, interovulatory interval, or circulating LH concentrations and 2) insulin was not detected in yolk sac fluid of 10 - 14 day equine conceptuses, investigators concluded that insulin is unlikely to be the signal of MRP in equids.[4] The role(s) of insulin (and hyperinsulinemia associated with endocrine disease) in reproductive dysfunction associated with EMS is not well described, with further work needed.

Serum concentrations of leptin, an adipokine produced primarily by white adipose tissue, have been positively correlated with body condition score (BCS) and degree of adiposity in many species, including humans, rodents and horses. Serum leptin concentration is considered to principally reflect body fat composition and to be a circulating 'marker' of adiposity (e.g. leptin concentration is directly related to body weight in Lusitano mares[5]). However, hyperleptinemia is also associated with systemic IR in horses (even when controlling for BCS), suggesting a more important role for leptin in pathophysiology of systemic ID in horses.

Overweight or obese mares have been reported to display continuous ovarian cyclicity (i.e. these mares often fail to enter seasonal anestrus) at a higher rate than lean mares, suggesting links among nutrition, glucose and lipid metabolism and reproductive function. Serum leptin concentrations correlated well with fat mass (which generally changes slowly), but they also may be altered more acutely by nutrition and medications. Hyperleptinemia remained stable when mares were exposed to varied management schemes (pasture versus hay in dry lots versus grain meal feeding), but variability in serum leptin concentrations was minimized when mares were fed hay (which also minimized variability in insulin and glucose concentrations).[6] Feed restriction for as little as 24 hours significantly lowered serum leptin concentrations in horses, which, due to the time course involved, was clearly not a result of significant reduction in body fat mass.[7] Leptin does not appear to be secreted in a pulsatile fashion in horses, but a circadian rhythm in its concentration has been reported;[8] furthermore, it has also been reported that leptin concentrations are lower in fasted versus fed states, but unaffected by ovariectomy or melatonin implants (making a direct link between leptin and the hypothalamo-pituitary- gonadal axis less clear). Leptin concentrations can also be manipulated pharmacologically; dexamethasone or propylthiouracil increase serum leptin concentrations in mares and geldings after a relatively short interval.[9,10] Treatment with clenbuterol for 6 months altered body fat and leptin concentrations in light breed mares in another study, with no effect on seasonal anestrus or cyclicity.[11]

Seasonality (especially occurrence and duration of seasonal anestrus) has been shown to be controlled to some extent by metabolic hormones and correlated with body condition. Older mares were more likely to cycle continuously and to enter seasonal anestrus later than younger mares in 1 study; the investigators reported that propensity for continuous cycling was associated with BCS, body fat percentage, and serum leptin concentration (all of which were highest in summer months).[12] Welsh pony mares (a breed likely more relevant to a discussion of ID and EMS than many light breeds, given recent descriptions of their genetic predispositions) fed to achieve low BCS always displayed seasonal anestrus, which persisted longer than in mares that were 'well fed' (only 40% of these mares displayed seasonal anestrus and it was shorter than in other groups).[13] There were large differences in growth hormone, IGF1, and leptin concentrations between well fed and restricted groups, and glucose, insulin, growth hormone and leptin concentrations were highly correlated with duration of ovulatory activity. However, in a population of mares NOT predisposed to ID/EMS, 'flushing' (i.e. acute increase in plane of nutrition, body condition score, and body fat percentage ~ 3 weeks prior to the breeding season) stimulated ovarian activity in stressed maiden Standardbred mares (and presumably improved their reproductive efficiency);[14] hormone concentrations were not evaluated, only first seasonal ovulation (which occurred earlier in mares with higher BCS).

Little information exists regarding the role of plane of nutrition and endocrine disease status on reproductive performance during pregnancy and lactation in horses. Feeding mares to obesity during gestation had no detectable effect on postpartum reproductive performance (interval to first and second ovulation after foaling, conception rates and early pregnancy loss rates were similar to mares maintained at a moderate BCS).[15] Even a high BCS produced by overfeeding during gestation did not seem to adversely affect postpartum reproductive performance in multiparous mares. Based on clinical experience, foals may have difficulty nursing (at least initially) from overconditioned mares that accumulate a large amount of adipose tissue within or near their mammary glands, which can efface the teats and make them less prominent and readily available to the foal. Additionally, mares with historical or current endocrinopathic laminitis may have increased orthopedic pain that is difficult to control as they gain weight during the third trimester. Even if reproductive efficiency itself does not suffer directly due to overconditioning, these welfare concerns for mare and foal are good reasons to maintain ideal BCS in broodmares during and after/before pregnancy.

Finally, in other species, robust evidence in multiple species supports a role for maternal nutrition and metabolism in 'programming' of future metabolic pathways of offspring while still in utero. Although fetal macrosomia is a common complication in children born to women with IR and diabetes mellitus (gestational or otherwise), children born prematurely to affected mothers, while initially often reported to have intrauterine growth restriction and low birth weight, later have significantly increased risk of obesity, IR, and type II diabetes mellitus in adulthood. Evidence for gestational programming in horses is very limited, but a few studies have investigated links between maternal and fetal/neonatal metabolism in equids. Leptin concentrations in nursing mares were shown not to affect leptin, triglyceride, or free fatty acid concentrations in their foals,[16] but maternal nutritional restriction during mid-gestation was associated with altered pancreatic responsiveness following birth in their (otherwise normal) foals.[17] In this study, mid gestational maternal nutritional restriction was associated with an increased acute insulin response to glucose (enhanced pancreatic ß cell responsiveness) in neonates, although no differences in response to ACTH stimulation or exogenous insulin administration was observed between foals from high-condition mares compared to those in moderate condition. The long-term significance of these findings remains to be determined, but this preliminary evidence for gestational metabolic programming in horses may represent another excellent reason for maintaining endocrine health of broodmares.

Medical management of broodmares with equine metabolic syndrome/insulin dysregulation

Optimization of nutrition and exercise management, as well as management of endocrinopathic laminitis if present, are mainstays of treatment for horses and ponies with EMS; strategies recommended for the general equine population can also be used for managing affected broodmares, particularly in the first and second trimesters of gestation (when metabolic demands and weight gain are not yet significantly different from the nonpregnant state). Indeed, these strategies may be appropriate for most broodmares, as IR is physiologic and progressive during normal pregnancy (this would be expected to be enhanced and more likely pathologic in animals that have been diagnosed with EMS before becoming pregnant). Provision of a diet primarily composed of grass hay (ideally containing < 10% nonstructural carbohydrate on a dry matter basis) and some sort of ration balancer to ensure adequate trace mineral and vitamin intake are central to dietary management of EMS cases; nutritional goals include minimizing dietary nonstructural carbohydrate (sugars, starches and fructans) and encouraging safe, gradual weight loss if needed. Although timing and rate of weight loss that is appropriate and safe for broodmares is currently unclear, prevention of excessive weight gain during gestation would seem to be a reasonable goal in this population. Continuous consumption of forage is considered ideal for horses and ponies in general, but timing of feeding was recently shown to affect fertility;[18] mares with continuous access to forage had higher rates of fertility and fewer estrus abnormalities than mares offered forage only at night. Continuous forage access may be important for maximizing fertility in broodmares generally, but particularly those who may have dietary restriction as a part of a treatment plan for EMS/IR. During the last third trimester and onset of lactation, most broodmares require supplemental calories in the form of concentrate feed to maintain body weight and support newly increased metabolic demands; composition of that diet can affect insulin sensitivity of the mare, even in the absence of a significant change in body weight or composition. In a study comparing effects of dietary composition on insulin sensitivity in broodmares, provision of a diet rich in sugar and starch enhanced systemic IR when compared to forage only or diet rich in fat and fiber; this effect was enhanced in mares with higher BCS.[19] The authors recommended using fat and fiber rich diets to provide supplemental calories in broodmares, in addition to avoiding overweight or obese body condition in this population; this recommendation seems particularly important when considering what is now known in horses and other species about gestational metabolic programming.[20-22]

Effects of exercise and medications on management of EMS and IR in broodmares have not been investigated, but these strategies might be useful as well. Exercise in particular may prove highly valuable, as it is likely safe (at least in the first and second trimesters, and as long as the animal is sound and comfortable), inexpensive, and highly effective in improving insulin sensitivity both acutely following an exercise bout and chronically in conjunction with weight loss and improvement in body composition. As little as 30 minutes of trot exercise daily is thought to be useful, as this amount of exercise elicits improvement in insulin sensitivity in the absence of any change in BCS or body weight in both lean and obese (though nonpregnant) mares;[23] this benefit was observed almost immediately following institution of the exercise program, but it did not persist long past discontinuation of the protocol. Consistency, therefore, appears to be important to maximize benefits from exercise.

Regarding pharmaceutical use in the management of broodmares with EMS, there are no studies of safety or efficacy of medications such as levothyroxine or metformin in pregnant horses and ponies. Based on known risks to the fetus associated with maternal hyperthyroidism in humans,[24,25] levothyroxine use during equine pregnancy should not be assumed to be empirically safe. The efficacy of metformin in improving IR in horses remains to be characterized more fully, but the drug appears to be reasonably safe in horses.[26] Metformin has not been evaluated for safety in pregnant mares; however, this drug is frequently used in diabetic pregnant women with an excellent safety profile.[27] If diet and exercise fail to achieve therapeutic goals in an at risk pregnant mare, metformin treatment may be helpful.

Effects of pituitary pars intermedia dysfunction on equine reproductive function

As equine populations age and as horse owners maintain health of their animals well into their third (and fourth) decades, the number of middle aged and geriatric horses presented for reproductive management will undoubtedly increase. Mares can conceive and carry foals well into their third decade, and this will certainly occur more commonly as management and medical progress increases the number of geriatric animals cared for by equine veterinary practices. Aged mares are more likely to require veterinary assistance for fertility issues. Even in the absence of a direct adverse effect of pars intermedia dysfunction (PPID) on reproductive performance, affected broodmares are likely to require veterinary management for an expected age-related decline in fertility; veterinarians will likely encounter these mares with increasing frequency in the future, making knowledge of PPID testing and treatment that much more relevant and important.

Although effects of PPID on equine reproductive performance have not been evaluated in great depth, it seems reasonable to assume that there should be some influence, given current understanding of the pathophysiology. The pars intermedia is involved in regulation of certain seasonal functions in equids (e.g. growing and shedding hair), and the seasonality of equine reproduction has also long been recognized; initial evidence was presented in 1979 that the pineal-hypothalamo-pituitary axis influences annual seasonal patterns of reproductive activity in horses.[28] Effects of cortisol and related metabolites on reproductive hormone secretion have long been held to negatively affect fertility; however, horses with PPID have inconsistently elevated serum cortisol concentrations and results of at least 1 study have suggested that even when cortisol secretion is high, effects on subsequent fertility are minimal (although mares diagnosed with PPID were not specifically evaluated).[29]

Dopaminergic neurodegeneration in certain subsets of hypothalamic neurons has been reported to be directly involved in pathogenesis of PPID, and pergolide (a dopaminergic agonist), is currently the recommended treatment for the disease. The role of dopamine in control of reproductive cyclicity in mares has been evaluated (albeit in otherwise normal mares, not those with PPID),[30] and it has been suggested that dopamine may facilitate control of reproductive seasonality in mares and exert tonic inhibition on reproductive activity during the anovulatory season. Therefore, whereas mares with PPID may cycle regularly (indeed, they may be more likely to cycle for a greater part of the year than normal mares; pharmacologic inhibition of dopaminergic neurotransmission resulted in increased follicular development and plasma estrogen and prolactin concentrations in mares),[31] effective treatment for PPID in the form of dopaminergic agonists may adversely affect cyclicity. Moreover, this treatment is highly likely to suppress prolactin secretion (in fact, protocols for induction of lactation in mares have been described using dopaminergic antagonists),[32,33] suggesting that hypogalactia and agalactia are more likely to be problematic in lactating mares receiving pergolide for treatment of PPID.[31]

Medical management of broodmares with pars intermedia dysfunction

Treatment of horses with PPID involves administration of medication to suppress secretory activity of pars intermedia (current FDA approved drug of choice is pergolide, a dopaminergic agonist) and management changes.[34] In pregnant and lactating animals, pergolide administration may increase the risk of prolonged gestation, premature placental separation and hypogalactia or agalactia. It may be appropriate in this case to manage PPID affected mares according to established recommendations for mares grazing endophyte-infested fescue pasture during gestation (also a condition caused by dopamine agonism);[35-37] strategies such as temporary discontinuation of pergolide therapy 30 days prior to the expected foaling date and judicious use of dopaminergic antagonists such as domperidone or sulpiride may be useful to prevent prolonged gestation and to encourage normal lactation. Mares should be monitored after foaling to ensure that they have adequate milk production; poor foal growth and incessant or continuous nursing behavior suggest that milk production may be inadequate and supplementation with milk replacer, goat's milk, and or a milk-based creep feed may be helpful. Pergolide therapy is often reinstituted at approximately 30 days after foaling; however, if the mare's PPID is poorly controlled without medication, she should receive treatment sooner, and alternative sources of nutrition for the foal should be investigated (including a healthy, lactating nurse mare). Alternatively, affected mares that don't tolerate withdrawal of pergolide therapy may be used most effectively as embryo donors if their genetics are sufficiently valuable. However, pergolide treatment might also be expected to affect oocyte and or embryo harvest from these mares. Further work is needed to optimize these protocols for mares with PPID to help guide best practice.

Although not all horses with PPID have systemic IR, this is not an uncommon finding in these animals.[38] Provision of sufficient calories to support lactation in IR horses (particularly those that have recently suffered a bout of laminitis) requires careful attention to composition of the diet to avoid inciting complications associated with hyperinsulinemia. Feedstuffs with calories primarily coming from fat and fermentable fiber should be offered, and sugars, starches, and fructans (non-structural carbohydrates) in the diet should be minimized. Body condition of affected mares should be carefully maintained within a normal range to ensure sufficient reserves to support lactation while avoiding over conditioning (excessive body weight would be expected to complicate clinical laminitis if it should occur, particularly in late gestation when body weight is already substantially increased).

Conclusion

EMS and PPID are very common conditions in horses and ponies (including those that are used for reproduction), and a concerted and extensive research effort over the past 20 years has yielded effective therapeutic and management strategies to minimize effects of these diseases on both length and quality of life and (preliminarily) reproductive efficiency in affected animals. Future work will improve upon these initial efforts and serve to generate best practices for optimizing reproductive efficiency for equids affected by endocrine disease.

Conflict of interest

The author claims no direct or indirect affiliation with any of the product manufacturers referenced in the body of this document and has no other conflicts of interest to declare.

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