Endocrinopathic laminitis and equine metabolic syndrome
H. L. Galantino-Homer
Department of Clinical Studies/New Bolton Center, School of Veterinary Medicine, University of Pennsylvania, Kennett Square, PA

Abstract
A common feature of equine laminitis is the dysfunction and failure of the dermal-epidermal attachment between the hoof wall and the distal phalanx, resulting in compromised digital support. Conditions that cause insulin resistance (IR) in horses, including obesity, equine metabolic syndrome (EMS), and pituitary pars intermedia dysfunction (PPID), greatly increase the risk of endocrinopathic laminitis (EL). Equine and human metabolic syndrome share some common features, including insulin resistance, regional adiposity, a pro-inflammatory state, and inflammatory and degenerative co-morbidities, with laminitis being the predominant co-morbidity in the horse. Epidemiological studies have identified many negative effects of IR and obesity on conception and pregnancy outcome in women. Studies are needed to determine the effects of IR on equine fertility. Broodmares might be at particular risk for EL due to the physiological decrease in insulin sensitivity associated with pregnancy. Previous laminitic episodes, insulin resistance due to obesity, EMS, or PPID, painful or stressful conditions, septic conditions, lack of exercise, exogenous corticosteroid administration, grazing high fructan content pasture, and high glycemic index feed supplementation should all be considered potential risk factors for EL that could have an additive effect with pregnancy-associated IR to push mares over the hypothetical insulin concentration threshold for laminitis induction. Strategies for the management of at-risk mares include diagnosis and treatment of EMS and PPID, weight and glycemic response management through diet and exercise, and therapeutic hoof trimming for mares with stable chronic laminitis. Mares with unstable chronic laminitis and/or inadequately controlled IR should be considered unfit for breeding.

Keywords: laminitis, insulin resistance, metabolic syndrome, equine, obesity

Equine lamellar anatomy and laminitis
As shown in Figure 1, the delicate structure of the epidermal and dermal lamellae of the normal equine foot greatly increases the surface area of dermal-epidermal attachment and forms the suspensory apparatus of the distal phalanx, facilitating the transfer of the horse’s weight from the skeletal elements of the digit to the hoof wall. Each foot has 550-600 parallel primary epidermal lamellae (PELs), each of which has 150-200 secondary epidermal lamellae (SELs) with an estimated total surface area for lamellar attachment of approximately 0.8 m² per foot. The reader is referred to other sources for more detailed information on the anatomy of this region.
Equine laminitis is a severe, debilitating and common disease of horses, often leading to the humane destruction of affected animals due to chronic pain and loss of use, and is recognized as a high priority topic for research by the United States Department of Agriculture and the American Association of Equine Practitioners. Several conditions, which have been recently reviewed, are associated with the development of laminitis, including alimentary carbohydrate overload, septic conditions, black walnut extract toxicity, excessive weight bearing or concussive forces to the foot, and the focus of this review, endocrinopathies resulting in IR and hyperinsulinemia (HI). Laminitis associated with IR or HI is collectively referred to as EL and is believed to include pasture-associated laminitis. In all forms, the initiating insult sets off a clinically silent developmental phase that is followed by acute laminitis. Signs of acute laminitis include shifting weight lameness, increased heat in affected feet, and bounding digital pulses. Once signs are present, lamellar damage may already be underway and the epidermal-dermal interface is weakened. The hallmark of laminitis is the loss of dermal-epidermal attachment between the epidermal lamellae of the inner hoof wall and the interdigitating dermal lamellae of the underlying distal phalanx. As shown in Figure 2, lamellar failure can result in displacement of P3 within the hoof capsule (failure of the digital suspensory apparatus) and chronic laminitis, or “founder”. Because the weight of the horse is primarily supported by the hoof wall via the lamellar attachment, unstable chronic laminitis causes secondary pathologies such as crushing of vasculature and neural tissue enclosed within the hoof capsule, osteolysis and fracture of the distal phalanx, and in the most severe cases, herniation of the distal phalanx through the sole of the hoof.

The lamellar epidermal cells undergo a wound healing response during laminitis that results in the generation of “lamellar wedge” or ectopic white line cornified epidermal tissue. This dysplastic tissue does not replace the mechanical functions of the original lamellae, might aggravate associated bone, vascular, and neural pathologies, and does not provide adequate barrier protection against ascending bacterial infections. We have demonstrated that the dysplastic lamellae in horses with chronic laminitis and a lamellar wedge is deficient in a marker of epidermal stem cell proliferative capacity, consistent with the abnormal growth and differentiation of this tissue. It is clearly preferable to prevent laminitis rather than to treat it.
Insulin resistance, inflammatory co-morbidities, and endocrinopathic laminitis

Many cases of equine laminitis are associated with insulin resistance and an equine metabolic syndrome that has many parallels to human pre-diabetic metabolic syndrome. Human metabolic syndrome, or syndrome X, is characterized by central obesity, atherogenic dyslipidemia (low high density lipoprotein-cholesterol (HDL-C), elevated low density lipoprotein-cholesterol (LDL-C) and serum triglycerides), a prothrombotic state, a pro-inflammatory state, hypertension, and IR, often culminating in β-cell failure, impaired glucose tolerance, and type 2 diabetes. Decreased insulin sensitivity or increased IR is defined as the decreased biological response of a nutrient to a given concentration of insulin at the target tissue, e.g. liver, muscle, or adipose tissue. Obesity is the most common risk factor related to IR. The list of human metabolic syndrome co-morbidities has grown in recent years and includes cardiovascular disease, hepatic steatosis, intramyocellular lipid accumulation, sleep apnea, osteoarthritis, psoriasis, and dementia and neurodegenerative diseases. A common feature of these co-morbidities is inflammation.
There are significant data supporting an association between insulin resistance and HI and equine laminitis.\textsuperscript{33-35} Insulin resistance in horses and ponies is typically associated with equine metabolic syndrome (EMS), equine Cushing’s syndrome/PPID, or corticosteroid treatment.\textsuperscript{14,36-38} Pituitary pars intermedia dysfunction is characterized by varying degrees of the following: excess adrenocorticotropic hormone (ACTH) and cortisol, hirsutism, polyuria/polydipsia, weight loss, muscle wasting, an abnormal fat distribution, insulin resistance, and high (>50%) incidence of laminitis.\textsuperscript{39} Equine metabolic syndrome is associated with regional adiposity with or without obesity.\textsuperscript{40} Horses and ponies with EMS are typically “easy keepers” that gain and retain weight easily and include over-represented “thrifty” breeds (ponies, Morgans, Paso Finos, Arabians, Saddlebreds, Quarter Horses, Tennessee Walking Horses, and domesticated Spanish mustangs).\textsuperscript{22,40} Regional adiposity commonly includes the neck (“cresty neck”), rump and tail head, and sheath in geldings or udder in mares.\textsuperscript{22,40} A “cresty neck” score has been developed for ponies and correlated with HI, hyperleptinemia, and an increased risk of pasture-associated laminitis.\textsuperscript{41,42} Obesity, increased cresty neck score, and HI have also been used to predict pasture-associated laminitis in horses.\textsuperscript{35}

Although these studies and clinical impressions are compelling, there is a need for more rigorous epidemiological data on risk factors for laminitis. A current epidemiological study at the University of Minnesota (http://www.cvm.umn.edu/equinegenetics/ems) is attempting to provide a more thorough phenotypic characterization of EMS and laminitis risk. A separate study initiated by the American Association of Equine Practitioners (AAEP) Research Foundation is generating epidemiological data on risk factors for pasture and endocrinopathy-associated laminitis (http://www.vetmed.tamu.edu/vmth/laminitis). It is likely that various factors that influence plasma insulin concentration or IR have an additive effect on a horse’s overall risk of EL.\textsuperscript{11} These factors may include those that lower the hypothetical threshold for laminitis induction, such as lamellar damage due to previous laminitic episodes or abnormal hoof conformation, and those that increase insulin concentrations toward the threshold. The latter may include IR due to obesity, EMS or PPID, painful or stressful conditions that increase the insulin counter-regulatory hormones (cortisol, epinephrine, norepinephrine),\textsuperscript{43} grazing high fructan content pasture and/or high starch feed supplementation,\textsuperscript{11,44} septic conditions,\textsuperscript{45} lack of exercise,\textsuperscript{46} exogenous corticosteroid administration,\textsuperscript{14,47} and pregnancy.\textsuperscript{47} The ongoing epidemiological studies will provide data regarding some of these putative risk factors.

A common feature of human metabolic syndrome, EMS, and PPID is IR and a pro-inflammatory state. Humans tend to progress to type 2 diabetes, but horses nearly always compensate for IR with increased β-cell insulin production resulting in HI, although diabetes mellitus also occurs in horses resulting in persistent hyperglycemia with glucosuria.\textsuperscript{22} Recently, studies utilizing a prolonged HI/euglycemic clamp, or HI model of experimental laminitis, have demonstrated that elevated insulin levels can induce laminitis in 48 h and 72 h in horses and ponies, respectively, by an unknown mechanism.\textsuperscript{48,49} The “inflammation hypothesis” of human metabolic syndrome states that obesity results in a shift of the leukocyte population in adipose tissue to pro-inflammatory CD8+ T cells and M1 or activated macrophages resulting in pro-inflammatory adipocytokine production.\textsuperscript{24,50} These factors impair insulin signaling, resulting in insulin resistance in adipose tissue, skeletal muscle and liver.\textsuperscript{23} Adipocytokines also create a chronic inflammatory environment that contributes to the generation of inflammatory and degenerative co-morbidities in humans. Two studies have reported increases in serum pro-inflammatory cytokines in horses with increased body condition score and percent body fat.\textsuperscript{51,52} In addition, impaired glucose transporter 4 (GLUT4) trafficking has been detected in muscle and adipose tissue from IR horses, consistent with impaired insulin signaling in these horses.\textsuperscript{53,54} Moreover, acute HI of only 6 h duration increased circulating plasma tumor necrosis factor (TNF) protein concentration and increased peripheral blood leukocyte IL-6 and IL-1β mRNA expression, consistent with the activation of pro-inflammatory cytokine production.\textsuperscript{55} In horses, the feet might be the organ system that is the most sensitive to this inflammatory environment, although the horses and ponies used for the HI model were not obese, and a more direct, toxic effect of the supraphysiologic serum insulin concentrations utilized for the model is implicated. The pathophysiology of HI laminitis and its relevance to naturally-occurring endocrinopathic laminitis are poorly understood, but could result from the activation of inflammation...
and/or cell proliferation. Proposed theories for HI-induced laminitis etiopathogenesis include vascular effects, activation of inflammation, disturbance in glucose metabolism, and direct insulin toxicity. A possible mechanism for insulin toxicity is via activation of insulin-like growth factor-1 receptor (IGF-1R), resulting in the promotion of epidermal hyperproliferation and cell survival.

**Insulin resistance and reproduction: Effect of pregnancy on insulin sensitivity**

Broodmares might be at particular risk for endocrinopathic laminitis due to the physiological effects of pregnancy on glucose and insulin dynamics. Mares with pre-existing IR or lamellar damage due to prior episodes of laminitis might be at or near the hypothetical HI threshold for induction of laminitis. Pregnancy in women and dogs is associated with a 60% and 43%, respectively, decrease in insulin sensitivity and an increased insulin response to glucose. This physiological IR of pregnancy facilitates glucose delivery to the fetus and is caused by the insulin counter-regulatory and post-receptor actions of progesterone, estradiol, growth hormone, placental lactogen, and placental cytokines. In women, elevated cytokine and lipid concentrations during pregnancy are believed to induce the IR of pregnancy through a post-receptor mechanism: defects in the intracellular insulin signaling pathway resulting in decreased ability of insulin to mobilize GLUT4 from the cytoplasm to the plasma membrane. Obese and overweight women are at increased risk for metabolic dysregulation in pregnancy resulting in gestational diabetes, pre eclampsia, and fetal overgrowth. Pregnancy is considered a metabolic stress test for the future risk of metabolic syndrome in women. It could be very informative to determine if, likewise, the insulin response to oral glucose tolerance test during equine pregnancy has any correlation with later development of EMS and/or laminitis in broodmares.

A recent study by George et al detected decreased insulin sensitivity and glucose effectiveness and higher acute insulin response to glucose in pregnant (28 weeks gestation) vs. nonpregnant Thoroughbred mares. The pregnant mares had prolonged hyperglycemia and HI in response to meal feeding that was particularly apparent following a high starch feed. Insulin resistance was not significant later (48 weeks gestation), although this may have been due to non-insulin-mediated glucose disposal from the mother to the growing fetus through placental facilitated diffusion of glucose, which results in an overestimation of maternal insulin sensitivity, particularly in late gestation. For mares that have underlying IR prior to pregnancy, the additional metabolic stress of pregnancy could greatly increase the risk of laminitis, although epidemiological studies are needed to verify this suspected risk. The laminitis case example shown in Figure 2 is from an obese mare that became acutely laminitic at approximately 90 days gestation and was eventually euthanized eight weeks later due to unstable chronic laminitis and unmanageable pain. The additive effects of obesity and pregnancy on IR might have initiated laminitis in this mare, and could possibly have been averted by weight management prior to breeding and by avoiding high starch feed and allowing exercise during pregnancy.

**Insulin resistance and reproduction: negative effects on fertility**

Not long ago, it was common practice to treat any overweight mare with perceived subfertility for hypothyroidism. The prevalence of hypothyroidism in adult horses is now believed to be very low. Many of the clinical signs previously attributed to equine hypothyroidism, which included obesity, regional adiposity, and weight gain on little feed, are now associated with EMS. In fact, horses that were made hypothyroid by surgical thyroidectomy or pharmacological suppression did not develop obesity or laminitis. In addition, two studies were unable to document any association between hypothyroidism and infertility in mares and thyroidectomized mares are capable of conceiving and carrying foals to term. Although previous over-diagnosis of hypothyroidism as the reason for treating mares with thyroid hormone supplementation may have been faulty, there is evidence that this therapy is useful, in combination with dietary restriction and exercise, in accelerating weight loss and improving insulin sensitivity.

In defining EMS, Johnson stated, “Affected broodmares sometimes exhibit abnormal estrous cycling, and are notoriously difficult to breed successfully”. However, few published studies have documented a link between EMS or obesity and reproductive abnormalities in mares. Mares with high
body condition score (BCS)\textsuperscript{72} are more likely to have continued estrous cyclicity and follicular activity during the winter compared to lean mares.\textsuperscript{73-76} Gentry et al reported increased winter serum luteinizing hormone (LH) concentration and response to gonadotropin releasing hormone (GnRH) in the high BCS mares, but no difference in weekly LH, follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), growth hormone (GH), glucose or insulin during the autumnal transition and winter anovulatory period.\textsuperscript{73} Vick et al reported significantly longer intervals between ovulations and prolonged luteal phases in obese mares (BCS = 7.5-9.0 on a scale of 1-9) compared with feed-restricted, previously obese mares (BCS = 4.0-5.0) during the late summer and autumn transitional period.\textsuperscript{76} In contrast, Waller et al did not detect any effect on ovarian activity, day of ovulation, and gonadotropin and progesterone concentrations for high BCS mares with hyperleptinemia, although the control mares also had high BCS in that study.\textsuperscript{75} A study using an experimental IR induction model resulted in no change in serum LH concentration or duration of luteal phase in treated mares, but did increase the interovulatory period and peak serum progesterone concentration.\textsuperscript{77} Information on the effect of high BCS or IR on hormone concentrations and reproductive characteristics during the breeding season, especially for older mares with naturally-occurring EMS, is lacking.

The effect of obesity on fertility in women has been much more thoroughly documented and readers are referred to a recent review.\textsuperscript{78} Obese women are three times more likely to suffer infertility than women with a normal body mass index.\textsuperscript{79} Proposed negative impacts of obesity on infertility include control of ovulation, oocyte development, embryo development, endometrial development, implantation, and pregnancy loss.\textsuperscript{78} Obesity, particularly central obesity, is associated with perturbations to the hypothalamic-pituitary-ovarian axis, menstrual cycle disturbance, oligo-/anovulation, and impaired response to assisted reproduction technologies.\textsuperscript{78} Insulin acts on the ovary via the IGF1 receptor to stimulate ovarian steroidogenesis and LH receptor upregulation.\textsuperscript{80} Insulin also enhances the sensitivity of pituitary gonadotroph cells to the action of Gn RH and modulates the bioavailability of the sex steroids via inhibition of hepatic sex hormone-binding globulin (SHBG) synthesis. Insulin resistance and HI leads to reduced SHBG, hyperandrogenemia, and disturbed IGF functionality, leading to menstrual and ovulatory disturbances.\textsuperscript{78} Studies are needed to determine the effects of EMS, IR and HI on mare fertility. When considered along with the risk of laminitis, potential effects on fertility provide additional impetus to aggressively treat and control EMS in mares prior to breeding and during pregnancy.

**Management of mares that are at risk for endocrinopathic laminitis**

Equine metabolic syndrome and EL risk should be managed through diagnosis of pre-existing laminitis, BCS and regional adiposity evaluation and monitoring, blood testing for endocrinopathic changes, and aggressive weight and serum insulin concentration normalization through diet, exercise, and, for refractory cases, thyroid hormone supplementation. Ideally, weight and insulin normalization should occur prior to breeding since the addition of pregnancy-associated IR to underlying IR could push the mare over the hypothetical insulin concentration threshold for EL.

As part of the breeding soundness evaluation or annual wellness examination should include screening for EMS and EL. Pre-existing, undetected laminitis is quite common, particularly in horses that are not being used for athletic endeavors, such as broodmares.\textsuperscript{46} Physical examination of the feet of these horses might detect the following: divergent laminitic growth rings (founder lines), dropped of flat sole(s), solar abscesses, widened white line at the toe, seedy toe, and/or sensitivity to hoof testers at the toe. Horses with suspected EMS and/or EL should have a carefully aligned lateromedial radiograph of the foot taken to determine if displacement of P3 within the hoof capsule has occurred, to serve as a baseline radiograph, and to guide decisions regarding corrective trimming and shoeing. BCS should be evaluated using the AAEP BCS score developed by Henneke et al, that ranges from 1 (poor) to 9 (obese).\textsuperscript{72} Horses with BCS ≥ 7/9 are at risk for EMS and EL. It is also possible to estimate body weight in pounds by measuring the heart girth and body length (point of shoulder to point of buttocck) in inches and applying the formula (heartgirth x heartgirth x body length)/330 = weight in pounds.\textsuperscript{46} Regional adiposity can be detected as cresty neck, enlarged udder, and fat around the tail head. Cresty neck can be assessed and monitored using the cresty neck score with a score of ≥ 3/5 suggestive of EMS,\textsuperscript{41,42} or by
dividing the distance along a line from the poll to the cranial aspect of the withers (x) by 4 and measuring
the neck circumference at 0.25x, 0.5x, and 0.9x.22

Blood testing should be performed on any horse with a history and physical findings consistent
with EMS or PPID. A fasting screening test can be performed by leaving one flake of hay after 10:00
p.m. and collecting blood in the morning prior to feeding. Pituitary pars intermedia dysfunction is
suspected if ACTH is >35 pg/ml, although elevated values are normal during the period of decreasing day
length (August, September, October in the northern hemisphere),81 and horses with elevated levels at that
time can be treated with pergolide and then re-evaluated in November after a two week withdrawal from
pergolide.46 A diagnosis of EMS is supported by a fasting insulin concentration >20 µU/ml and fasting
leptin concentration > 7 ng/ml, although the latter assay is not commercially available at this time.22 An
elevated fasting glucose >110 mg/dl is also consistent with EMS or could be evidence of diabetes
mellitus. Clinical signs and these fasting values are adequate for diagnosis of EMS, but if the results are
equivocal, dynamic testing using a combined intravenous glucose-insulin test or oral sugar test, as
described,22 should be performed.

Equine metabolic syndrome, PPID, obesity, and HI should be controlled prior to breeding due to
the risk of EL. Pituitary pars intermedia dysfunction is treated with pergolide starting at 1 mg/day orally
and rechecking serum ACTH and insulin after one month, the goal being ACTH < 70 pg/ml with a dosage
range of 1-5 mg pergolide/day. Obesity and EMS should be managed by limiting grazing with a grazing
muzzle or limited turn-out and avoiding pasture in the spring and fall when the non-structural
carbohydrate (NSC) content is the greatest.44 A weight loss regimen should be instituted that includes
feeding a grass hay with analyzed NSC content of less than 10% (dry matter basis) fed at 1.5% of ideal
body weight per day with vitamin and mineral supplementation and reduced to 1% of ideal body weight if
no weight is lost after one month.22 Exercise promotes weight loss and improves insulin sensitivity and
should be part of the program.82 If the horse cannot be ridden or lunged, at the very least, it should have
turn out in a small grass paddock with a companion since social interaction increases activity.22 Ideally,
exercise consisting of a minimum of 30 min at a trot or canter, four to seven days/week, should be
instituted.22,46,82 For lame horses, some benefit can be derived from hand walking.46 Obviously, the
pregnant broodmare presents a difficult challenge since feed supplementation is indicated at least for the
last trimester to support rapid fetal growth at that time.83 Based on the findings of George et al, a high
fat/high fiber feed is recommended for broodmares with EMS to reduce the glycemic and insulinemic
response, although more research is needed on this topic.47

If the horse is either refractory to the weight loss regimen or is perceived to be at high risk of, or
already suffering from EL, thyroid hormone supplementation with levothyroxine can be instituted as an
aide for weight loss and to normalize insulin concentrations more rapidly.22,46 Short term treatment (three
to six months) is recommended at 0.1 mg/kg or 48 mg/day for horses weighing 450-525 kg.22

Due to the potential catastrophic consequences of EL during pregnancy, the veterinarian and
owner must work together to manage obesity and EMS and prevent EL. Owners should be strongly urged
not to breed mares with existing obesity, endocrinopathy, or EL until weight and insulin concentrations
have been normalized and the laminitis is stabilized.

References
Pract 2010;26:29-49.
2. Leach DH, Oliphant LW. Ultrastructure of the equine hoof wall secondary epidermal lamellae. Am J Vet Res
1983;44:1561-570.
3. Bragulla H: Fetal development of the segment-specific papillary body in the equine hoof. J Morphol 2003;258:207-
224.
4. Bragulla H, Hirschberg RM: Horse hooves and bird feathers: two model systems for studying the structure and
development of highly adapted integumentary accessory organs - the role of the dermo-epidermal interface for the


60. de Laat MA: The investigation of insulin-induced laminitis in horses The University of Queensland, School of Veterinary Science; 2011.


<table>
<thead>
<tr>
<th>Citation</th>
<th>Reference</th>
</tr>
</thead>
</table>