

# Metabolic Syndrome in the Pregnant Mare

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Metabolic syndrome is a term drawing together a seemingly disparate set of clinical findings in human patients, these including insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, and atherosclerosis. Obesity is a common but not consistent finding. The term has been subsequently applied to horses with obesity, insulin resistance, hyperinsulinemia, and dyslipidemia. A chronic pro-inflammatory condition is thought to exist in metabolic syndrome, the most important sequelae of the condition in the horse being laminitic. The effects on pregnancy in the mare have not been elucidated; however, in humans, gestational diabetes, abortion, and fetal compromise have been shown to result. Author's address: Rood and Riddle Equine Hospital, PO Box 12070, Lexington, KY 40580; e-mail: pmorresey@roodandriddle.com © 2012 AAEP.

## 1. Introduction

The concept of metabolic syndrome in the horse, while relatively new, is widely researched and reviewed.<sup>1</sup> In other species, including humans, the profound effects of excessive adipose tissue have been well documented, and this obesity is considered a key component in development of the metabolic syndrome. Metabolic syndrome was introduced as a diagnostic category to identify human individuals at risk of developing type 2 diabetes and atherothrombotic cardiovascular disease.<sup>2</sup> This term has come to be applied to equines with obesity, insulin resistance, and hyperinsulinemia.

Studies involving the metabolism of the pregnant mare have revealed that insulin resistance is in fact a normal occurrence in the healthy pregnant mare enabling redirection of maternal nutrients to the developing fetus. However, in mares with metabolic syndrome, any metabolic abnormalities and endocrinopathies existing before the pregnancy is established will probably be exacerbated.

## 2. What Is Going on in Metabolic Syndrome?

Insulin resistance was first proposed as a cause of glucose intolerance, elevated insulin levels, dyslipidemia, and hypertension in humans over 20 years ago.<sup>3</sup> Metabolic syndrome has developed from this concept, being defined as a combination of cardiovascular risk factors including such diverse components as visceral adipose accumulation, insulin resistance, hyperinsulinemia, hypertension, chronic inflammation, microalbuminemia, and a prothrombotic disorder leading to endothelial cell dysfunction and atherosclerosis.<sup>4</sup> Research has largely centered on human subjects due to the increasing occurrence of metabolic syndrome and the serious cardiovascular effects associated with this condition. In the horse, while sharing many of the same components, laminitis is the condition of primary concern due to its potentially lethal sequelae. Considerable debate exists regarding the etiology and pathogenesis of metabolic syndrome, as no single unifying mechanism has been

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## NOTES

elucidated.<sup>5</sup> A complex interaction between genetics, hormonal status, and nutrition is most likely.

Adipose tissue is not simply a store of excess energy but is rather an organ of diverse functions that plays a pivotal role in development of metabolic syndrome.<sup>6</sup> Adipokines, biologically active secretions of adipose tissue, may play a role in the pathogenesis of insulin resistance, as some have been shown to have effects on insulin sensitivity and signaling.<sup>7</sup> Adiponectin has antidiabetic effects and may be a novel therapy in metabolic syndrome.<sup>8</sup> In contrast, resistin and tumor necrosis factor- $\alpha$  increase as pregnancy progresses, which is in contrast to levels of adiponectin. These levels correlate with the state of reduced insulin sensitivity often developed in the latter stages of pregnancy.<sup>9</sup>

### 3. Presentation in the Equine

#### Body Score

In the horse, overall body adiposity may not be indicative of metabolic syndrome, as the nuchal ligament adipose depot has been shown to have unique biological behavior with a greater tendency to contribute to inflammatory mediator production than other fat stores.<sup>6</sup> Therefore, visceral fat may not contribute to the pathogenesis of obesity-related disorders in the horse as it does in other species.

#### Laminitis

Insulin resistance is associated with obesity in horses, and this is considered to be a contributing factor to the onset of pasture-associated laminitis in horses with metabolic syndrome.<sup>10-12</sup> The feeding of high starch diets has also been associated with insulin resistance and hyperinsulinemia, thereby increasing the risk of laminitis.<sup>13,14</sup>

### 4. What Can We Learn From Pregnancy in Other Species?

In humans, pregnancy has been shown to increase requirements for insulin secretion concurrently with increasing insulin resistance, thus raising demands on pancreatic  $\beta$  cells and promoting gestational diabetes.<sup>15,16</sup> This physiological insulin resistance promotes transfer of glucose from the mother to the fetus.<sup>17</sup> Because glucose is the main energy substrate for the fetoplacental unit, any alterations in maternal glucose and insulin profiles may affect fetal development.<sup>18,19</sup> As pregnancy advances, the response by insulin to glucose increases, but the sensitivity to insulin decreases.<sup>9,20</sup> Insulin sensitivity in normal pregnant women was found to be reduced to one-third that of nonpregnant women.<sup>17</sup> By this means, the body is prepared for the impending demands for growth of the placenta and fetus.

Polycystic ovary syndrome (PCOS) is considered a prediabetic state; women with PCOS also have features of the metabolic syndrome, including insulin resistance, obesity, and dyslipidemia, suggesting an

increased risk for cardiovascular disease.<sup>21</sup> Also, PCOS has been associated with the development of gestational diabetes; these patients enter pregnancy with increased insulin resistance when compared with normal women.<sup>22</sup> Gestational diabetes is thought to result when pancreatic  $\beta$  cells are unable to overcome the extra demands of physiological insulin resistance in addition to their pre-existing elevated insulin resistance.<sup>15,23,24</sup> Women who have PCOS before the onset of pregnancy have increased rates of first-trimester spontaneous abortion compared with normal women.<sup>23</sup>

Effects of gestational diabetes do not end at delivery.<sup>25</sup> In the short term, neonatal complications such as hypoglycemia, hypocalcemia, hypomagnesemia, hyperbilirubinemia, and polycythemia are reported and are thought to be the result of hyperinsulinemia, hypoxemia, and prematurity at delivery of the fetus. In the long term, increased rates of childhood and adolescent obesity, impaired glucose tolerance, or diabetes mellitus are seen. Control of maternal glucose concentrations before conception and during pregnancy have been shown to reduce congenital malformations, fetal macrosomia, birth trauma, and neonatal respiratory distress syndrome in neonates born to diabetic mothers.<sup>25</sup>

### 5. What Is Happening in the Normal Late Pregnant Mare?

Marked changes in carbohydrate metabolism and pancreatic  $\beta$ -cell function occur during pregnancy in the mare, in common with other researched species. Pregnant mares consuming high starch feeds in the third trimester have increased insulin and glycemic responses to feeding than nonpregnant mares or matched pregnant mares consuming a fat and fiber-based diet.<sup>26</sup> Hyperinsulinemia, increased pancreatic  $\beta$ -cell sensitivity to glucose, and increased resistance to the action of insulin occur.<sup>20</sup>

Glucose uptake by the fetoplacental unit is dependent solely on the concentration gradient between the maternal and fetal circulations across the placenta.<sup>27</sup> No increase in glucose uptake by the fetus occurs during pregnancy; the increased requirements for growth and development during gestation are met solely by redirection from maternal tissues. After periods of fasting, the sensitivity to glucose of the pancreatic  $\beta$  cells is reduced, thus allowing preferential transfer of glucose to the fetus by limiting maternal uptake.<sup>20</sup>

Up to approximately 270 days of gestation, enhanced pancreatic  $\beta$ -cell sensitivity to glucose results in hyperinsulinemia.<sup>20</sup> This allows both fetal and maternal requirements to be met without inducing hypoglycemia. After this period, the fetus gains approximately 45% of its final birth weight and consequently has a high absolute glucose demand.<sup>28</sup> Uterine glucose uptake removes 75% of that lost from the maternal circulating pool.<sup>29</sup> Maternal glucose usage is therefore reduced to a minimum to allow this transfer to the developing fetus. Insulin

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concentrations and pancreatic  $\beta$ -cell sensitivity to glucose are also reduced compared with earlier in gestation.<sup>20</sup>

Fetal metabolism and development is affected in utero by alterations in maternal metabolism.<sup>30</sup> Furthermore, these alterations affect insulin secretion in response to glucose in the neonatal foal that had maternal midgestational nutrient restriction.<sup>31</sup>

It should therefore now be realized that insulin resistance is a normal occurrence in the pregnant mare, one that enables redirection of maternal nutrients to meet the high demands of the developing fetus.

## 6. Effects of Metabolic Syndrome on the Maintenance of Equine Pregnancy

The unstable dynamics of glucose levels in the late-term mare bears clinical consideration. Hypoglycemia in late pregnancy has been associated with increased uterine PGF<sub>2a</sub> metabolite levels and possible premature delivery.<sup>32</sup> Therefore, any period of prolonged hypoglycemia in late gestation, such as may occur with fasting during management of a colic episode, has the potential to initiate fetal expulsion.

Although unproven in the mare, consideration should be given to control of metabolic syndrome before the initiation of pregnancy. Abortion may result, as has been proven in early gestation of human fetuses, with a reduction seen in first trimester spontaneous abortion in women with metformin usage.<sup>33</sup> There has been no evidence of teratogenic effects on the fetus with this approach.<sup>34,35</sup> An improvement in early pregnancy rates has been reported with the use of metformin in mares showing clinical signs compatible with metabolic syndrome.<sup>a</sup>

Pre-existing endocrine dysfunction may be exacerbated by metabolic syndrome. The decrease in insulin sensitivity during gestation, the promotion of hyperinsulinemia, and the proinflammatory state will increase the likelihood of complications such as laminitis in the pre-Cushingoid mare with subclinical insulin resistance possibly already present. Circulating thyroid hormone levels may be reduced, leading to a spurious diagnosis of hypothyroidism.

## 7. Management

### Nutrition

Control of gestational diabetes in women has been aided by dietary control. Insulin sensitivity has been shown to increase with weight loss in obese individuals.

In the horse, the provision of a low starch, high fat, and fiber diet has been shown beneficial to insulin dynamics during gestation.<sup>26</sup> Hay or a hay substitute is probably the only form of energy intake required. Supplementation with a ration balancer is important. Success of long-term dietary control of metabolic system relies on the elimination of feeds rich in non-structural carbohydrates. Removal of

grain, sweet feeds, restricted access to pasture, and a diet based on grass hay is required.<sup>36</sup>

### Exercise

Studies in humans have investigated the relationship between physical activity energy expenditure, aerobic fitness, obesity, and the progression toward metabolic syndrome or diabetes, with exercise shown to have a protective role.<sup>37</sup> Programs involving concurrent dietary management and exercise lead to increased weight loss. In the horse, there are conflicting results as to the success of an exercise program.<sup>36</sup> Body weight and fat percentage can be decreased; however, effects on insulin sensitivity are variable. If laminitic changes allow, exercise should be beneficial.

### Medications

Management of preconception obesity and insulin resistance, dietary control, glucose monitoring, oral hypoglycemic agents, judicious insulin therapy, fetal monitoring, and timing of delivery to minimize the risk of dystocia have been the cornerstone of management of gestational diabetes in women.<sup>38</sup> In contrast, management of metabolic syndrome in the horse has predominantly centered on the use of a small number of pharmacological agents.

Metformin is an oral antidiabetic drug of the biguanide class. Widely prescribed in human medicine as a first line drug for the treatment of type 2 diabetes in obese patients, it is also prescribed for conditions where insulin resistance is a factor including PCOS and gestational diabetes. Usage during pregnancy has been shown to improve insulin resistance in hyperinsulinemic PCOS women, with the most benefit seen in those with the greatest insulin resistance and endocrinopathy before conception.<sup>39</sup>

Insulin has a major role in the regulation of ovarian steroidogenesis, follicular development, and granulosa cell proliferation.<sup>40</sup> The insulin-like growth factor system is therefore affected, and, as this has been shown crucial to follicle selection and dominance in the mare, disturbances of ovarian function may be seen.<sup>41,42</sup> Obese mares with reduced insulin sensitivity have been shown to have prolonged interovulatory and luteal phases.<sup>43</sup> A parallel between PCOS in women and disturbances of follicular dynamics in mares can therefore be drawn.

Spontaneous first trimester abortion in women with PCOS was reduced from 73% to 10% with metformin usage in one study<sup>33</sup> and from 62% to 26% in another.<sup>23</sup> Weight gain during pregnancy for women maintained on metformin was markedly reduced, decreasing the risk of gestational diabetes. While on metformin, the frequency of gestational diabetes and preeclampsia in women with PCOS did not differ from normal control pregnancies.<sup>44</sup> In addition, testosterone is lowered in pregnant women with PCOS, removing the risk of fetal virilization.<sup>39</sup>

A modulation of the natural increase in insulin resistance during pregnancy is noted, with fasting insulin levels at the third trimester of pregnancy not significantly different from the last measurement before conception.<sup>44</sup> There has been no evidence of teratogenesis with use of metformin during gestation or as a result of prior usage.<sup>45</sup>

In the horse, investigation into the usefulness of metformin in the control of the insulin resistance of metabolic syndrome has been controversial. Pharmacological studies showed that the drug does not reach plasma levels considered to be therapeutic, albeit at the established human concentrations.<sup>46</sup> Short-term improvement in insulin sensitivity and pancreatic  $\beta$ -cell function was noted in one study.<sup>47</sup> However, metformin was not shown to be an effective long-term monotherapy for increasing insulin sensitivity in horses in another study.<sup>43</sup>

Side effects of metformin usage in humans have been reported to include decreased birth weight; however, when correcting for pregnancy complications, this change was not significant compared with healthy control subjects.<sup>48</sup> Gastrointestinal side effects have been reported, consisting of nausea and diarrhea.<sup>49</sup> Deleterious effects in the horse have not been reported.

L-thyroxine is familiar to equine practitioners as a standard treatment for suspected hypothyroidism in the horse. Documented cases of hypothyroidism in the horse are rare, with suspected clinical signs minimal and the confounding presence of nonthyroidal illness affected circulating thyroid hormone levels in the absence of thyroid gland pathology.<sup>50,51</sup> It is thought that supplementation with L-thyroxine actually has a positive therapeutic effect through its actions in the improvement of function of other hormones, chiefly insulin.<sup>51</sup>

Oral administration of L-thyroxine is well tolerated and has been previously shown to induce weight loss and increase insulin sensitivity from pretreatment levels in euthyroid mares.<sup>52,53</sup> In another study, long-term L-thyroxine was shown to diminish the acute insulin response to glucose administration, with similar effects on body weight and insulin sensitivity as shorter-term studies.<sup>54</sup>

Oral glucose-lowering (hypoglycemic) compounds are widely used in the management of human hyperglycemia and metabolic syndrome.<sup>34,55,56</sup> In the horse, this class of compounds has not been widely reviewed. Pharmacokinetic evaluation of one compound (pioglitazone) has been reported, with the medication approaching therapeutic levels in the horse.<sup>57</sup>

Magnesium deficiency has been shown to be associated with insulin resistance. Intracellular magnesium has been shown to play a key role in regulating the action of insulin, insulin-mediated cellular glucose uptake, and vascular tone. A reduction in intracellular magnesium concentration promotes defective tyrosine-kinase activity, post-

receptor impairment in insulin action, and a worsening of insulin resistance in diabetic patients. Therefore, magnesium deficiency has been proposed as a possible underlying unifying mechanism of the insulin resistance found in a number of metabolic conditions. Low dietary magnesium intake is also related to the development of type 2 diabetes.<sup>58</sup> Supplementation with oral magnesium was shown to improve insulin sensitivity in hypomagnesemic type 2 human diabetic patients<sup>59</sup>; however, the benefits of supplementation have not been repeatable in all clinical studies.<sup>58</sup> Magnesium supplementation has been associated in other studies with improved insulin sensitivity.<sup>60,61</sup> The beneficial effect of magnesium with respect to insulin sensitivity is thought to result from the enhancement of intracellular signaling and increased tyrosine kinase activity via calcium channel blockade.<sup>62,63</sup>

In the horse, few studies have been performed to evaluate the effect of magnesium supplementation. In one study, administration of a supplement containing both chromium and magnesium did not alter blood variables or insulin sensitivity in this study of laminitic obese horses.<sup>64</sup> While the benefits of additional magnesium are unproven, it is prudent to ensure that at minimum the established maintenance requirements are met.

Chromium has been widely used in both human and equine medicine in an effort to control insulin resistance and hyperinsulinemia. In humans, it was discovered that patients had development diabetes mellitus while receiving total parenteral nutrition, and affected individuals benefited from chromium supplementation.<sup>65</sup> Chromium is thought to elicit its effects by enhancing intracellular postinsulin receptor signaling pathways.<sup>66</sup> This may occur through enhanced tyrosine kinase activity or reduced tyrosine phosphatase activity, which prolongs the effects of insulin binding to its receptor and thereby increases insulin sensitivity.<sup>66</sup> Chromium supplements are taken by patients with insulin-resistant or type 2 diabetes mellitus, and both chromium picolinate and chromium chloride lower fasting plasma glucose concentrations, increase insulin sensitivity, and reduce requirements for oral antidiabetic drugs in humans.<sup>60,61</sup> Evaluation of chromium administration in the horse has resulted in variable results.<sup>67,68</sup>

Pergolide in itself is not a treatment for metabolic syndrome, although many Cushingoid (pituitary pars intermedia dysfunction or PPID) horses are insulin resistant and benefit from treatment of the concurrent precipitating pituitary condition. Chronic laminitis is common in horses suspected of PPID, and they display other signs such as hirsutism, supraorbital fat, and abnormal body fat distribution.<sup>69</sup> Until recently, pergolide was available only as a compounded suspension of varying potency and stability, with these factors shown to be affected by storage conditions.<sup>70</sup> Pergolide is now available in a tablet form<sup>b</sup> that is the only federally approved formulation.

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## 8. Management of Concurrent Conditions

Dietary management to alleviate obesity will aid in the management of insulin insensitivity, which is the driving force behind the proinflammatory state of the affected horse. Chief among the complications of this syndrome is laminitis. Aggressive and early management of this condition is paramount to a successful case outcome.

The pathophysiology and treatment of laminitis has been extensively reviewed.<sup>71-74</sup> Medical management will include judicious use of anti-inflammatories, analgesics, and supportive care. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is widespread, with phenylbutazone at standard dose rates being commonly used.<sup>75</sup> Prolonged courses of NSAIDs are likely to be necessary to provide sufficient analgesia during the convalescent phase. Care must be taken to avoid complications such as right dorsal colitis in these cases.<sup>76</sup> Cryotherapy has become first-line treatment in acute cases, the rationale being inhibition of matrix metalloproteinase enzyme activity, responsible for enzymatic remodeling of the lamellae.<sup>71</sup> The opinion of the author is that it is never too early to consult a farrier or podiatrist in the management of the laminitic insulin resistant horse.

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<sup>a</sup>Lu K. Personal communication, 2012.

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Orig. Op.	OPERATOR:	Session	PROOF:	PE's:	AA's:	COMMENTS	ARTNO:
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