Metabolic diseases – do we really know if they affect reproduction?
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Abstract
Conditions affecting metabolism (including endocrine dysfunction) intuitively have wide-ranging effects on potentially all body functions. In many species metabolic and endocrinological changes have been proven to have significant effects on female reproductive processes, with ovarian activity, establishment of pregnancy, pregnancy maintenance to term and the overall health of the fetus impaired. Effects on the reproductive competence of the male are also known to occur. With respect to the conceptus itself, life-long alterations in metabolic processes are found in the offspring of affected females when compared to non-affected cohorts. The presence of insulin resistance with hyperinsulinemia and the subsequent generation of a chronic proinflammatory state appears to be the genesis of these problems. In horses details regarding the effects of metabolic and endocrine dysfunction on reproductive competence remains largely unknown however potential for alteration can be inferred due to similarities in reproductive physiology between species. Clinical observations of individuals support the likelihood of metabolic and endocrine dysfunction detrimentally affecting equine reproductive efficiency.

Keywords: Metabolic, endocrine, pituitary, hyperinsulinemia, proinflammatory, cyclicity, pregnancy

Introduction
Metabolic syndrome describes a set of clinical findings in human patients including insulin resistance, hyperinsulinemia, dyslipidemia, hypertension and atherosclerosis, however obesity while common is not a consistent finding. A chronic pro-inflammatory condition is thought to exist in 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. This term has come to be applied to equines suffering from obesity, dyslipidemia, insulin resistance and hyperinsulinemia.

Pituitary pars intermedia dysfunction (PPID, or more commonly Cushing’s syndrome) is a common condition of aged horses and ponies in which inhibition of the intermediate lobe of the pituitary is lost due to degeneration of the hypothalamic dopaminergic neurons. During the early stages of this syndrome cellular hyperplasia of the intermediate lobe results in increasing levels of pro-opiomelanocortin (POMC), a precursor molecule cleaved into many peptides including α-melanocyte stimulating hormone (α-MSH), adrenocorticotropic hormone (ACTH), -endorphin and corticotropin-like intermediate lobe peptide (CLIP). As the syndrome progresses the pars intermedia enlarges until a singular intermediate lobe adenoma develops that compresses the adjacent pituitary and hypothalamic structures. Furthermore, a relationship between the onset of metabolic syndrome and PPID is anecdotally reported. Many PPID horses are insulin resistant, this being theorized to be a result of obesity, chronic hyperinsulinemia, or insulin resistance.

What is going on in metabolic syndrome and PPID?
Insulin resistance was first proposed as a cause of glucose intolerance, elevated insulin levels, dyslipidemia, and hypertension in humans over 20 years ago. 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.

Adipose tissue is not simply a store of excess energy, but is rather an organ of diverse functions which plays a pivotal role in development of metabolic syndrome. 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.\textsuperscript{5} It is the resulting hyperinsulinemic proinflammatory state that is thought to drive the laminitis seen in affected horses.

Considerable debate exists regarding the etiology and pathogenesis of metabolic syndrome as no single unifying mechanism has as yet been elucidated.\textsuperscript{6} A complex interaction between genetics, hormonal status and nutrition is most likely. The concept of metabolic syndrome in the horse while relatively new is widely researched and reviewed.\textsuperscript{7}

In PPID, following loss of hypothalamic dopaminergic inhibition acting on the pituitary, increased synthesis of POMC peptides and proliferation of melanocytes occurs. Increased ACTH secretion can lead to hypercortisolemia which has profound effects on metabolic and immune function. It is thought the altered secretion of prolactin and the gonadotrophic hormones may potentially be responsible for effects on reproductive function. Hypertrichosis, chronic infections, loss of muscle mass, abnormal fat deposition, slow wound healing, polyuria and polydipsia, and lethargy are the common clinical signs. Many PPID horses are also insulin resistant.

Additionally, horses with metabolic syndrome or PPID may be clinically indistinguishable in the early stages of either condition as both may display abnormal adiposity and hyperinsulinemia with hyperglycemia.

**Are there proven reproductive effects of metabolic syndrome or PPID in other species?**

**Ovarian function**

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, and is characterized by hyperandrogenic chronic anovulation.\textsuperscript{8} The PCOS is considered a pre-diabetic state with affected women displaying features of metabolic syndrome including insulin resistance, obesity, and dyslipidemia, suggesting a heightened risk for cardiovascular disease.\textsuperscript{9} Insulin has a major role in the regulation of ovarian steroidogenesis, follicular development and granulosa cell proliferation.\textsuperscript{10} Insulin resistance has been recognized as the major factor related to PCOS, with compensatory hyperinsulinemia stimulating ovarian androgen production and the peripheral aromatization of androgens to estrogens, altering gonadotropin secretion and therefore follicular development.\textsuperscript{11}

**Pregnancy**

The PCOS has been associated with the development of gestational diabetes with affected women entering pregnancy with increased insulin resistance compared to normal women.\textsuperscript{12} Subjects that have PCOS prior to the onset of pregnancy have increased rates of first trimester spontaneous abortion compared to unaffected women.\textsuperscript{13}

Human pregnancy raises requirements for insulin secretion simultaneously with increasing insulin resistance, raising synthetic demands on pancreatic cells and promoting development of gestational diabetes.\textsuperscript{14,15} With advancing pregnancy the response of insulin to glucose increases, however sensitivity to insulin decreases.\textsuperscript{16,17} Insulin sensitivity in healthy pregnant women was found to be reduced by two-thirds when compared to that of non-pregnant women.\textsuperscript{18} The resulting physiological insulin resistance promotes transfer of glucose from the mother to the fetus.\textsuperscript{18} By this means, the body is prepared for the impending demands for growth of the placenta and fetus.

**The human male**

Significant hormonal differences occur between subfertile obese and fertile males of normal body weight.\textsuperscript{19} Obesity has been shown to effect sperm production with sperm concentration decreased in highly obese men, and a continuous decrease associated with advancing age.\textsuperscript{20} Total testosterone is decreased with obesity, however estradiol is not affected leading to a decrease in the testosterone:estradiol ratio which influences the hypothalamic-pituitary axis.\textsuperscript{21} Resulting suppression of testicular function can therefore feed back in a self-reinforcing cycle. Furthermore, the relative decrease in muscle mass and
increase in body fat resulting from decreased testosterone promotes obesity, insulin resistance, and further functional pituitary suppression.22

Metabolic syndrome and the mare

Ovarian function

Metabolic syndrome affects the insulin-like growth factor system, this being crucial to follicle selection and dominance in the mare, leading to disturbances of ovarian function.23,24 Obese mares with reduced insulin sensitivity have been shown to have prolonged interovulatory and luteal phases.25

What is happening in the normal late pregnant mare?

Marked changes in carbohydrate metabolism and pancreatic 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 non-pregnant mares or matched pregnant mares consuming a fat and fiber based diet.26 Hyperinsulinemia, increased pancreatic cell sensitivity to glucose, and increased resistance to the action of insulin occur.16

Glucose uptake by the fetoplacental unit is dependent solely on the concentration gradient between the maternal and fetal circulations across the placenta.27 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. Following periods of fasting, the sensitivity to glucose of the pancreatic cells is reduced, this allowing preferential transfer of glucose to the fetus by limiting maternal uptake.16

Up to approximately 270 days of gestation, enhanced pancreatic cell sensitivity to glucose results in hyperinsulinemia.16 This allows both fetal and maternal requirements to be met without inducing hypoglycemia. Following this period, the fetus gains approximately 45% of its final birth weight and consequently has a high absolute glucose demand.28 Uterine glucose uptake removes 75% of that lost from the maternal circulating pool.29 Maternal glucose usage is therefore reduced to a minimum to allow this transfer to the developing fetus.16 Insulin concentrations and pancreatic cell sensitivity to glucose are also reduced compared to earlier in gestation.16 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 the developing fetus.

Effects of metabolic syndrome on the maintenance of equine pregnancy

The effects on pregnancy of metabolic syndrome in the mare are not proven, however in humans gestational diabetes, abortion and fetal compromise have been reported.12,13 Interestingly, a reduction is seen in first trimester spontaneous abortion in women with metformin usage,30 and no evidence of teratogenic effects on the fetus with this approach has been reported.31,32 An improvement in early pregnancy rates has been reported with the use of metformin in mares showing clinical signs compatible with metabolic syndrome (Dr. Kristina Lu, personal communication).

Metabolic syndrome and the stallion

As in the mare, reproductive effects of metabolic syndrome have not been clearly defined, although there is a wealth of comparative information available. It has been shown that there is an interaction between metabolic syndrome and testicular function that is bidirectional in nature. Obesity can affect spermatogenesis and alterations in the hypothalamic-pituitary testicular axis occur. Resulting endocrine function changes in the testes have been shown to impact systemic metabolic parameters.

PPID and reproductive disorders

Mares with PPID may suffer from persistent uterine infections that are challenging to clear. However cyclical activity may continue and mares without uterine infection can be bred successfully. In others, cyclic irregularities (anestrus, delayed ovulation) may be present. If these mares are bred,
anecdotal reports indicate a lower likelihood of carriage to term and delivery of a healthy foal. In non-pregnant mares, serous mammary secretions may occur regardless of previous lactation status, with this theorized to be a manifestation of excessive prolactin secretion.

The use of the dopamine agonist pergolide may allow restoration of appropriate cyclicity and a pregnancy may be established. If carried to term, agalactia following delivery (due to prolactin antagonism) is possible. As a result, it is a common recommendation that pergolide therapy be discontinued between two and four weeks prior to the expected foaling date. Anecdotally, the author and others have maintained pregnant mares on pergolide throughout gestation without detriment to foal delivery or adequate milk production. Information on the reproductive effects of PPID in stallions is not available.

Summary

The ability to quantify the reproductive effects of metabolic syndrome and PPID is limited due to the difficulties in definitively diagnosing either condition at this time. However, consideration of comparative reproductive physiology strongly supports anecdotal observations in the horse regarding disturbances in cyclicity, pregnancy establishment and maintenance, and spermatogenesis as a result of metabolic or hypothalamic-pituitary disturbances.

References