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Energy endocrine physiology, pathophysiology, and nutrition of the foal

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Most homeostatic systems in the equine neonate should be functional during the transition from intra- to extrauterine life to ensure survival during this critical period. Endocrine maturation in the equine fetus occurs at different stages, with a majority taking place a few days prior to parturition and continuing after birth. Cortisol and thyroid hormones are good examples of endocrine and tissue interdependency. Cortisol promotes skeletal, respiratory, cardiovascular, thyroid gland, adrenomedullary, and pancreatic differentiation. Thyroid hormones are essential for cardiovascular, respiratory, neurologic, skeletal, adrenal, and pancreatic function. Hormonal imbalances at crucial stages of development or in response to disease can be detrimental to the newborn foal. Other endocrine factors, including growth hormone, glucagon, catecholamines, ghrelin, adipokines (adiponectin, leptin), and incretins, are equally important in energy homeostasis. This review provides information specific to nutrition and endocrine systems involved in energy homeostasis in foals, enhancing our understanding of equine neonatal physiology and pathophysiology and our ability to interpret clinical and laboratory findings, therefore improving therapies and prognosis.

The equine neonate has specific nutritional needs during the critical transition from fetal to extrauterine life. Because of limited energy storage and the dependency of the foal on rapid initiation of suckling to provide immunity and nutrition during the first few hours of life, nutritional intervention is often necessary. Additionally, critical illness often leads to endocrine dysregulation, which has wide-ranging effects on energy homeostasis. Understanding the maintenance of energy homeostasis, consequences of critical illness, and nutritional needs of the foal is therefore important for the equine practitioner. The objectives of this document are to review factors that might impact energy homeostasis in healthy and sick newborn foals, including endocrine regulation and nutritional management.

Energy Homeostasis

Several organs and cells with endocrine functions are involved in energy homeostasis, including the pancreas (α- and β-cells), fat (adipocytes), hypothalamus (multiple nuclei), pituitary gland (pars distalis), adrenal gland (cortex, medulla), stomach (glandular cells), intestine (K and L cells), thyroid gland (follicular cells), liver (hepatocytes), and bone (osteoblasts). Therefore, energy regulation in the equine fetus and neonate involves complex interactions among multiple endocrine axes, particularly while transitioning to consuming mare's milk shortly after birth. This is a common period for energy dysregulation in sick neonatal foals, highlighting the importance of understanding energy homeostasis and the nutritional needs of the equine neonate.

The equine fetus is highly dependent on the maternal transfer of glucose,[1] with major increases in glucose utilization from mid gestation to 300 days, matching umbilical glucose uptake but not total energy demands.[1,2] The rate of glucose uptake has been estimated to be around 7 mg/kg per minute by 290 days of gestation, which follows a pattern similar to oxygen consumption and CO_2 production.[3] This substantial rate of transplacental glucose transfer should be the basis for initial feeding (6 to 8 mg/kg/min) for newborn foals, depending on disease status.

Per body weight, glucose utilization decreases after day 180 of gestation, in part due to maximal placental transfer capacity.[1] It is possible that the reduced rate of glucose transfer to the equine fetus at the end of gestation, together with restricted uterine space and endocrine changes around this period, contribute to the duration of pregnancy.[1,4]

An infrequently discussed energy source for the equine fetus is L-lactate, which significantly increases in late pregnancy.[1,2] As glucose transfer reaches its limit, L-lactate from the placenta fills part of this energy gap. Glucose and free fatty acid (FFA; nonesterified fatty acid [NEFA]) concentrations are lower, while L-lactate concentrations are higher in fetuses compared to their dams in most mammalian species, including the horse.[1,5] Foals are born with high L-lactate and NEFA but low glucose concentrations. Fructose concentrations are high in the equine fetus, but its source and metabolic fate are

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uncertain.[6] The equine placenta is lipid permeable, in particular to FFAs,[7] but the placenta also synthesizes lipids from glucose in late gestation to be used by the fetus.[2,8]

Fructose, lipids, and amino acids may be valuable sources of energy for the fetus; however, based on oxygen utilization and nutritional studies,[1,2,8-10] it appears that after glucose, lipids may be the next most important fuel for the equine fetus in late pregnancy. Based on urea production, amino acid oxidation could account for up to 15% of equine fetal oxygen consumption.[1] Equine fetuses in late gestation have a low capacity to produce glucose, and glycogenic capacity is limited due to low hepatic and renal glycogenic enzyme activity[11]; therefore, foals are often born hypoglycemic, with minimal energy reserves (low glycogen and adipose tissue) and limited time to adapt.[1,11,12]

Maintaining normoglycemia immediately after birth can be challenging; thus, rapid caloric intake and utilization are essential for survival. This requires functional endocrine systems that rapidly regulate energy homeostasis. In addition, the gastrointestinal tract must be functional to handle the rapid load of nutrients from colostrum and milk. The foal must become efficient at converting lactose into galactose and glucose, translocating glucose into cells to become a rapid source of energy, use it efficiently, store it, and reduce energy waste. There are many aspects of energy homeostasis in the equine neonate that remain unclear, in particular, processes involved in gluconeogenesis, glycogenolysis, glycogenesis, and lipolysis. Fatty acids and amino acids in colostrum and milk are important fuels and could have regulatory functions during the transition to extrauterine life. This is noted when contrasting equine colostrum and milk composition and caloric density.[13,14] In addition, mare's colostrum contains cytokines and growth factors that play important biological functions, including gastrointestinal development, immunity, and endocrine modulation.

Endocrine Physiology of the Foal

The following section reviews the endocrine regulation of energy homeostasis in the foal. Functions and interactions among energy-regulating hormones in the neonatal foal are summarized **(Table 1)**.

The endocrine pancreas

The islet of Langerhans is the functional unit of the endocrine pancreas. Five cell types are present in the islets (α-, β-, δ-, ε-, and γ-cells) and secrete glucagon (α-cells); insulin, amylin, and C-peptide (β-cells); and somatostatin (δ-cells); ε-cells produce ghrelin; and γ-(PP)-cells release pancreatic polypeptide (PP). Insulin and glucagon are the primary pancreatic hormones.

Insulin is the main hormone controlling energy metabolism and storage. Its secretion is stimulated by hyperglycemia, certain amino acids, cortisol, growth hormone (GH), and cholinergic stimulation and suppressed by hypoglycemia, somatostatin, ghrelin, and adrenergic agonists. Glucagon has opposing actions to insulin, on energy metabolism with its main targets being the liver and adipose tissue. Its main function is to increase glucose concentrations during hypoglycemia by promoting glycogenolysis and gluconeogenesis. The equine neonate has unique aspects regarding glucagon release in the immediate postpartum period.[15] Specifically, nursing stimulates its release. Insulin is the only hormone that prevents hyperglycemia, while glucagon, epinephrine, and cortisol avert hypoglycemia.

Foals are born with a functional pancreas, which is central to the disposal of carbohydrates, amino acids, and fatty acids.[16-20] In the newborn foal, insulin-induced hypoglycemia activates the adrenal medulla, adrenal cortex, and adenohypophysis to release catecholamines, cortisol, adrenocorticotropic hormone (ACTH), and GH and increases FFA and lactate concentrations,[21] likely to enhance the availability of other sources of energy.

Basal insulin concentrations change minimally in the equine fetus at the end of gestation,[8] but the β-cell response to exogenous glucose increases from 270 days of gestation to term.[17,20] In 1 study,[22] resting insulin concentrations were similar between presuckle (before colostrum) and 1- to 2- and 10- to 12-day-old healthy foals. Insulin concentrations before birth, at birth, and 1 week after birth were lower in foals compared to their dams.[17,22] Duration and frequency of nursing were negatively associated with insulin concentrations in these foals.[22]

It has been proposed that foals are born in an insulin-resistant state due to peripartum increases in cortisol concentrations[16,21,23]; however, this effect may be short-lived based on recent work from our lab, showing that low doses of insulin (0.02 IU/kg, IV) have hypoglycemic effects in 1- to 3-day-old foals.[24] Insulin also resulted in hypoglycemia in 2- to 4-day-old foals born to mares that experienced illness during pregnancy.[25] In contrast, another study[26] noted minimal insulin response to hyperglycemia in 2-hour-old foals, suggesting that other endocrine factors peaking around this time (within hours of birth), such as cortisol and epinephrine, interfere with insulin secretion.[27,28]

The intrauterine environment and caloric intake by the dam might influence insulin sensitivity and secretion in the foal.[16,25,26,29] Insulin sensitivity was similar between foals born to mares fed high- or low-starch diets; however, over time, foals from high-starch-diet dams had reduced insulin sensitivity.[29] Nutrient restriction due to illness in mid pregnancy enhanced insulin sensitivity in foals born to mares in moderate compared to high body conditions.[25] No difference in insulin secretion was found in foals from overfed mares; however, they had increased islet number and size.[26] Foals overgrown in utero had higher basal insulin concentrations and greater β-cell response to glucose.[16] This suggests that the nutritional programming of fetal β-cells is influenced by the maternal nutritional plane, illnesses, and intrauterine growth rate.

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Table 1—Hormonal control of energy homeostasis.

Hormone	Stimulated by	Suppressed by	Actions on energy homeostasis
Insulin	Hyperglycemia Amino acids Glucocorticoids[a] GH Cholinergic stimulation GIP GLP-1	Hypoglycemia Somatostatin Ghrelin Glucocorticoids Leptin Adrenergic stimulation	↑ Glycogenesis ↑ Glycolysis ↑ Fatty acid synthesis ↑ Protein synthesis ↑ Glycogen synthesis ↓ Glycogenolysis ↓ Gluconeogenesis ↓ Ketogenesis ↓ Lipolysis
Glucagon	Hypoglycemia Amino acids Nursing Catecholamines GIP	Hyperglycemia GLP-1 Somatostatin Insulin	↑ Glycogenolysis ↑ Gluconeogenesis ↑ Lipolysis ↑ Energy expenditure ↓ Lipogenesis
Cortisol[b]	Stress via ACTH Hypoglycemia-delayed response at birth Peripartum HPAA activation Catecholamines	Glucocorticoids	↑ Glycemia ↑ β cell maturation ↑ Insulinemia[a] ↑ Lipolysis ↑ Fat redistribution ↑ Glucagon secretion ↑ Gluconeogenesis ↑ Glycogenolysis ↓ Insulin secretion ↓ Insulin sensitivity ↓ Glycogenesis ↓ Inflammation*
Epinephrine	Hypoglycemia (after 7 days of life) Glucagon Glucocorticoids		↑ Glycemia ↑ Glycogenolysis ↑ Gluconeogenesis ↑ Glucagon secretion ↑ Lipolysis ↓ Insulin secretion
GH	GHRH Ghrelin Hypoglycemia Insulin Stress	Somatostatin IGF-1 Hyperglycemia Fatty acids Glucose	↑ IGF-1 ↑ Glucose ↑ Glycogenolysis ↑ Gluconeogenesis ↑ Lipolysis ↑ Amino acid uptake ↑ T4 → T3 conversion ↓ Insulin sensitivity
GIP	Enteral glucose Amino acids Fatty acids	Lack of luminal nutrients	↑ Insulin secretion ↑ Glucagon secretion ↑ Insulin sensitivity ↓ Gastric emptying ↓ Gastrin secretion ↓ β cell apoptosis
GLP-1	Enteral glucose Amino acids Fatty acids Neurotransmitters	Lack of luminal nutrients Glucocorticoids	↑ Insulin secretion ↑ Insulin sensitivity ↓ Glucagon secretion ↓ Gastric emptying ↓ β cell apoptosis ↓ Food intake ↓ Cytokine production[c]
IGF-1	GH	IGF-1 Cytokines	Mediates GH actions ↓ GH secretion

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Table 1 (*continued*)

Hormone	Stimulated by	Suppressed by	Actions on energy homeostasis
Leptin	Insulin Lipid storage Feeding Amino acids Glucocorticoids	GH Fasting Catecholamines	↑ Insulin sensitivity ↑ Glucose uptake ↑ Lipolysis ↑ Fatty acid oxidation ↑ Hepatic insulin extraction ↑ Energy expenditure ↓ Appetite ↓ Body weight ↓ Insulin secretion ↓ Gluconeogenesis ↓ Lipogenesis ↓ Glucagon secretion ↓ Inflammation[c] Modulates HPAA Modulates HPGA[c]
Adiponectin	Insulin Physical activity Catecholamines	Cytokines (IL-1β, IL-6, TNF-α) Glucocorticoids Fasting Ghrelin	↑ Insulin sensitivity ↑ Glucose uptake ↑ Glycolysis ↑ Fatty acid oxidation ↑ Energy expenditure ↓ Body weight ↓ Lipogenesis ↓ Gluconeogenesis ↓ Glycogenolysis ↓ β-cell apoptosis ↓ Inflammatory cytokines[c]
Ghrelin	Fasting	Feeding GH IGF-1 Glucose Fatty acids Amino acids Insulin Somatostatin Glucocorticoids Leptin	↑ Appetite ↑ Glycemia ↑ Body weight gain ↑ GH release ↑ Gastric motility ↓ Insulin secretion ↓ Insulin sensitivity ↓ Inflammation*

GH = Growth hormone. GHRH = GH-releasing hormone. GIP = Glucose-dependent insulinotropic polypeptide/gastric inhibitory peptide. GLP-1 = Glucagon-like peptide-1. HPAA = Hypothalamus-pituitary-adrenal axis. HPGA = Hypothalamus-pituitary-gonadal axis. T3 = Triiodothyronine. T4 = Thyroxine. TNF-α = Tumor necrosis factor-α.

[a]Even though glucocorticoids (cortisol) decrease insulin secretion, they can lead to hyperinsulinemia by interfering with insulin signaling and subsequent insulin resistance. In the equine fetus, cortisol is required for maturation of the β-cells and insulin secretion. [b]Cortisol mediates the actions of the HPAA. [c]Not directly related to energy homeostasis.

A functional hypothalamus-pituitary-adrenal axis is central to the maturation of the equine endocrine pancreas and thyroid gland. Equine fetuses with low cortisol concentrations have a poor insulin response to hyperglycemia compared to those with normal or high cortisol concentrations.[19] This cortisol effect was not evident with arginine challenge, indicating that cortisol is more important for β-cell maturation and carbohydrate sensing, enabling β-cells to regulate glycemia in the immediate postnatal period.[19] This is part of the rationale for administering dexamethasone to high-risk mares at the end of gestation.

The mechanisms controlling glucagon secretion in response to hypoglycemia in the equine fetus do not appear to be well-developed until birth, although α-cells respond rapidly to intravenous arginine.[30] This difference between α- and β-cell response to glucose implies that in preparation for extrauterine life, a functional β-cell is necessary for rapid glucose disposal. One can speculate that gluconeogenic mechanisms may not be as mature and a glucagon response to amino acids may be important to promote gluconeogenesis immediately after birth, considering the minimal hepatic energy reserves in newborn foals.[11] It is also possible that catecholamines contribute to glucagon secretion near term in anticipation of postpartum hypoglycemia as both epinephrine and norepinephrine peak around the same time.[8]

One study in healthy newborn foals showed minimal changes in glucagon concentrations in response to fasting for 180 minutes, while insulin concentrations decreased steadily until foals were allowed to nurse.[15] In response to nursing, glucagon

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concentrations doubled within 30 minutes, which was a surprising finding.[15] In the same foals, insulin concentrations increased to 3-fold prenursing values.[15] The fact that both α- and β-cells had a rapid response to nursing indicates that there are regulatory mechanisms in the equine neonatal endocrine pancreas that remain to be elucidated, in particular when these hormones are considered counterregulatory. It is possible that milk carbohydrates or incretins promoted insulin release while milk amino acids or fatty acids triggered glucagon secretion. Another factor contributing to glucagon secretion is glucose-dependent insulinotropic polypeptide (GIP), an intestinal peptide in high concentrations in newborn foals that stimulates glucagon secretion.[31]

In sick neonatal foals, hypoglycemia is more frequent than hyperglycemia, and both are linked to mortality.[32,33] Septic foals often have low insulin,[32,34] but increased glucagon, triglyceride, and NEFA concentrations,[32,34] reflecting endocrine and metabolic responses to energy needs. Glucagon increases in sick foals to promote gluconeogenesis, glycogenolysis, and lipolysis. Low insulin concentrations in septic foals are likely a response to hypoglycemia; however, in foals with hyperglycemia, low insulin values should be considered inadequate.[35] These foals usually are unable to regulate glycemia and may require insulin therapy. This is also an indication of disease severity that often results in death.

The enteroinsular axis

The enteroinsular axis (EIA) comprises intestinal factors that stimulate the endocrine pancreas to secrete insulin and include GIP (K cells), glucagon-like peptide-1 (GLP-1; L cells), and glucagon-like peptide-2 (GLP-2; L cells). These factors are known as incretins, which are the basis for a new generation of drugs to treat diabetes. GLP-1 and GIP have synergistic actions over β-cells to enhance insulin secretion; however, GLP-1 inhibits while GIP stimulates glucagon release. GLP-2 mainly has enterotrophic actions, important in regulating nutrient absorption and maintaining mucosal morphology. The EIA is more important than glucose in promoting insulin secretion in humans.[36]

Newborn foals have a functional EIA that is more responsive to nutrients compared to horses.[31,37] Nursing promotes a stronger EIA response (GIP, GLP-1, and insulin release) than enteral glucose or lactose administration in foals.[31] Nursing is also a strong stimulator of glucagon secretion in newborn foals.[15,31] This indicates that, in addition to carbohydrates, other factors in milk (e.g., amino acids, fatty acids) contribute to the communication between the intestine and the endocrine pancreas. This information could have clinical relevance in future strategies to manage critically ill or orphan foals lacking proper enteroinsular activation secondary to intestinal dysfunction, which may develop hyperglycemia due to inappropriate β-cell stimulation and insulin response. Pancreatic β-cells could also be refractory to incretins during sepsis. This could in part explain low insulin concentrations measured in septic foals.[32]

Information on the EIA in sick foals is minimal. A study[35] showed that septic foals have high GLP-1 and GLP-2, but low-insulin concentrations, despite normo- to hyperglycemia, suggesting a disconnect between the intestine (incretins) and insulin secretion (β-cells), potentially leading to glucose intolerance in critically ill foals (e.g., hyperglycemia). Plasma GIP concentrations were lower in septic foals compared to healthy foals and followed a pattern similar to insulin.[35] Based on this information, it has been proposed that different mechanisms may contribute to reduced insulin secretion in critically ill foals.[35]

Growth hormone, IGF-1, ghrelin, leptin, and adiponectin

The somatotropic axis (hypothalamic-pituitary-somatotropic axis) consists of GH from the pituitary gland and insulin-like growth factor-1 (IGF-1; somatomedin-1) from the liver. The secretion of GH is regulated by growth hormone-releasing hormone (GHRH) and growth hormone-inhibiting hormone (GHIH; somatostatin) from the hypothalamus and ghrelin from the stomach and brain. This system is also relevant to energy homeostasis during energy deprivation (hypoglycemia is a potent stimulus for GH release), where it makes different substrates available to be used as fuel.

Most actions of GH are mediated via IGF-1; an increase in GH secretion is followed by elevations in IGF-1 concentrations. IGF-1 suppresses GH secretion. Growth hormone has anti-insulin properties, while IGF-1 has insulin-like actions.[38,39] Growth hormone increases insulin concentrations by stimulating its synthesis and secretion, interfering with its actions, and promoting hyperglycemia.[40] Blood concentrations of GH and IGF-1 increase in foals over time.[41,42] Ghrelin concentrations increase in response to anorexia to promote hunger, stimulate GH release, and inhibit insulin secretion to make energy available. Critically ill foals have increased ghrelin and GH but reduced IGF-1 concentrations, which is consistent with impaired somatotropic axis signaling.[43] This phenomenon was termed "somatotropic axis resistance,"[43] which is likely a consequence of systemic inflammation.

Leptin, an adipocyte-derived hormone (adipokine), is considered the main regulator of satiety. It is an anorexigenic factor, and its blood concentrations correlate with total body fat in horses and other species.[44,45] Leptin promotes insulin sensitivity and insulin hepatic extraction, and decreases insulin secretion (adipoinsular axis) and glucose concentrations.[46] Insulin stimulates leptin secretion by adipocytes. A key function of the adipoinsular axis is to inhibit insulin secretion to reduce adipogenesis. In foals, leptin concentrations increase after birth to decline a few days later.[47] The role of leptin in foal disorders remains unclear but is likely important considering its actions on various aspects of energy homeostasis. Minimal leptin differences were found between sick and healthy foals, but concentrations were lower in nonsurvivors.[32]

Adiponectin, another adipocyte-derived peptide hormone (adipokine), is negatively correlated

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with body condition in horses and other species.[45,48] Adiponectin increases insulin sensitivity, glycolysis, and fatty acid oxidation. Blood adiponectin concentrations were not different between sick and healthy foals,[49] and their role in energy dysregulation remains unclear.

Nutritional Considerations of the Foal

Placental metabolism and the equine fetus

The placenta is the interface between the mare and fetus (fetomaternal unit), transporting oxygen, minerals, and nutrients, removing waste products, and processing substrates required for placental metabolism and fetal growth.[2] It is highly metabolic, with higher oxygen consumption rates compared to the mare and fetus.[50] It is responsive to homeostatic challenges, evoking a stress response in the mare and fetus, and adapts to fetal nutrient demands.[51-53] Placental tissue metabolizes several substrates, diversifying sources of carbon and nitrogen to ensure adequate fetal growth and differentiation.

Maternal glucose is the main carbohydrate used by placental tissues.[2] Placental production of carbohydrates other than glucose (i.e. fructose, lactose) may serve as alternative substrates for uteroplacental tissues and fetal growth during energy deprivation (i.e. maternal illness). The placenta can transport, utilize, produce, and interconvert amino acids. Fetoplacental amino acid metabolism is complex, involving metabolic cycling between maternal, fetal, and placental compartments. For example, the equine placenta synthesizes glutamine from branched-chain amino acids and glutamate to be used for fetal needs.[2,54]

Lipids and FFAs are required for the growth and development of fetoplacental tissues; however, the epitheliochorial placenta of horses is less permeable to these substances compared to other species. Their concentrations are negligible in equine uterine and umbilical circulations during late gestation. To meet fetal needs, the equine placenta can hydrolyze esterified lipids into fatty acids. Together with placental synthesis of lipids from glucose and keto acids, this provides an adequate supply of essential fatty acids to fetoplacental tissues.

Nutritional programming

Fetal metabolic programming studies[55] in humans have shown that gestational diabetes, undernutrition, and overnutrition during gestation can lead to metabolic disease later in life for children. These disorders are mainly the result of changes in metabolic programming from epigenetic modification.[55] Similar phenomena have been documented in horses, concluding that imbalanced nutrition during gestation can have negative metabolic, reproductive, and orthopedic consequences for the offspring later in life. For the purpose of this review, the nutritional effects leading to alterations in metabolism and other endocrine abnormalities will be discussed.

Pregnant mares are often fed high-starch diets to ensure the metabolic demands of pregnancy. Diets with high caloric density can contribute to insulin resistance in equids. George et al[29] showed that foals of mares fed high-starch diets (39% starch) late in gestation had higher baseline glucose and insulin concentrations and decreased glucose disposal (glucose effectiveness). This confirms that mare nutrition in gestation influences fetal glucose homeostasis and insulin secretion. These foals at 160 days of age had lower insulin sensitivity compared to foals of mares fed low-starch diets (4% starch), suggesting negative long-term implications of the mare's diet during gestation.

Studies on the mechanisms altering metabolism and glucoregulation in foals from maternal overnutrition are scarce. In other species, excessive maternal caloric intake affects offspring pancreatic mass and β-cell size and increases insulin production, all indicators of insulin resistance. One study[26] found that foals exposed to maternal overnutrition (40% higher than National Research Council recommendations for late gestation mares) during maximal fetal growth had an increase in size and number of pancreatic islets, consistent with β-cell compensation. This study[26] indicates that maternal overnutrition predisposes offspring to adult-onset metabolic disease. It also emphasizes the importance of appropriate nutrition during gestation to prevent adult endocrine and metabolic disorders, such as insulin dysregulation and laminitis.

Maternal illnesses also affect fetal development. Foals born to mares with illness-induced weight loss had lower birth weights and higher cortisol responses to ACTH compared to foals born to healthy and appropriately fed mares.[25,56,57] A high plane of nutrition before and after illness-induced undernutrition appeared to be protective against an exaggerated insulin response to glucose in these foals.[25] These aspects of maternal nutrition are important, having long-term effects on the foal and practical implications for mare and foal management.

Nutritional requirements of the foal

After birth, the neonatal foal has a high metabolic rate and little to no reserves in the form of glycogen or fat,[11,58] contributing to an inability to survive nutritional deprivation. Compared with other species, hepatic glycogen stores in the foal are minimal[11] and only support thermoregulation up to an hour postpartum.[59,60] After this time, energy is derived from fat stores, which is also limited in the newborn foal.[13,59]

Healthy foals consume approximately 15% of their body weight in milk on the first day of life,[13,61] to steadily increase to 25 to 30% over the first week of life, equating to 120 to 150 kcal/kg/day to support a rapid growth rate of 1 to 1.3 kg/day.[13,61] This amount equates to 10 to 12.5 liters of milk per day for a 50-kg foal.[13] Milk consumption decreases from 25% of body weight in the second week of age to 20% by 1 to 2 months of age.[61] Thoroughbred foals attain approximately 80% of their adult height and nearly

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50% of their adult weight by 6 months of age, where most rapid growth occurs.[62]

Most information regarding the feeding behavior of foals is from observational studies, measurements of milk consumption, and evaluation of milk composition.[13,58,61] Neonatal foals nurse approximately 5 times per hour, and by 3 months of age, the frequency decreases to around 4 times per hour.[63] Ideally, foals should suckle each teat equally. Mares begin to naturally wean their foals by 16 to 24 weeks of age, terminating nursing sessions earlier.[63]

The composition of a mare's milk changes throughout lactation to support the nutritional needs of the growing foal. Colostrum contains 1,000 kcal/kg of digestible energy (DE), 19% protein, 0.7% fat and 5% lactose.[13] Early in lactation (weeks 1 to 4), mare's milk contains 480 kcal/kg of DE, 2.7% protein, 1.8% fat, and 6.2% lactose.[13] By weeks 9 to 21 of lactation, DE is relatively similar (420 kcal/kg), protein and fat concentrations decrease (1.8 and 1.4%, respectively), and lactose concentrations increase slightly (6.5%). Compared to cow's milk, mare's milk contains lower DE, protein, and fat concentrations but higher lactose concentrations.[13] Breed and individual horse variations in milk composition have been observed.[13,61] Diet impacts mare's milk composition and, therefore, affects foal nutrition.[64] For example, mares fed diets supplemented with corn oil and fiber had a better fatty acid profile and higher immunoglobulin G concentrations compared to those fed diets supplemented with starch and sugar (corn and molasses).[64]

Nutritional Considerations in the Sick Foal

Nutritional requirements in the critically ill foal

The nutritional needs and energy requirements of critically ill neonatal foals are less clearly understood. When feeding a sick foal, it is important to consider the type of disease, maturity, metabolic status, glycemia, gastrointestinal function (tolerance to enteral feeding), route, type of diet (mare's milk, replacer), and cost. It has been assumed that nutritional requirements of critically ill neonatal foals were higher due to a hypermetabolic state secondary to systemic inflammation and increased energy consumption.[58] However, Jose-Cunilleras et al[65] showed that daily resting energy requirements (RER) of critically ill foals were lower (40 to 50 kcal/kg/day; ~10% of body weight) than healthy foals and foals without life-threatening illnesses, and RER in hospitalized increased prior to discharge (60 to 80 kcal/kg/day).[65] Sample calculations for both enteral and parenteral nutrition in the sick foal are provided for clarity **(Appendix 1)**.

The most recognized aspect of foal nutrition is the need for colostrum ingestion and immunoglobulin absorption within the first 24 hours of life. However, colostrum is also a calorie-dense source of energy for the equine neonate, containing approximately twice as much energy than mare's milk.[13] Additionally, there are many factors in colostrum that are important for immune function. Ensuring adequate transfer of passive immunity is key to preventing neonatal diseases. In addition, colostrum supplementation may be necessary for foals that could not nurse or are born to mares with no or minimal amount of colostrum. Donor colostrum or mare's colostrum should be administered via a nasogastric tube in foals with a functional gastrointestinal tract (GIT). Ideally, this should be administered in 3 to 4 500-ml feedings within the first 6 to 12 hours of life, although larger feedings are possible.

Enteral nutrition

The decision to provide enteral versus parenteral nutrition in sick foals is very important, with many considerations, including practicality, facilities, foal's clinical condition, and cost. The enteral route is generally preferred, as it provides trophic factors for normal GIT development, function, and integrity and minimizes bacterial translocation.[66,67] It is important to determine if the foal has normal GIT function. Signs of colic, abdominal distention, nasogastric reflux, or diarrhea prompt the withholding of enteral nutrition. Abdominal auscultation or ultrasonography can be used to assess GIT motility. Enteral feeding should be reduced or withheld if there are signs of ileus. Measuring abdominal circumference frequently during hospitalization is a more objective and practical method to assess tolerance to enteral feeding. If enteral feeding is deemed appropriate, starting with small amounts (roughly 25% of calculated RER [discussed above]) is advised and increasing slowly as long as the foal continues to tolerate nutrition. The ideal nutrition is mare's milk or donor mare's milk, but commercial milk replacers are available that closely approximate mare's milk composition.

Feeding foals from a bowl feeding pan or via an indwelling feeding tube is preferred versus a bottle to prevent aspiration of milk and subsequent pneumonia. Evaluation of the foal's suckle reflex and swallowing should precede feeding. A feeding tube is recommended if the foal's suckle reflex is uncoordinated, weak or absent. A 14-French, 100- to 125-cm feeding tube may be placed into the distal esophagus. Foals may not cough when the tube is in the trachea, so confirming correct placement is important and can be done via palpation of the tube in the esophagus, endoscopy, or radiography. The feeding tube can be sutured to the nostril and secured to the muzzle with tape. Educating caretakers on the use of the feeding tube is important. The free end of the tube should be closed to avoid the aspiration of air. Applying syringe suction on the tube prior to milk administration is important to check for placement (negative pressure) and nasogastric reflux (not more than 50 ml of reflux). The foal should be in sternal recumbency or standing during milk administration (and 10 to 15 minutes after feeding) to prevent aspiration. Milk should be delivered by gravity flow and flushed with 10 to 20 ml of water to clear the tube.

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Feeding should start at no more than 5 to 10% of body weight per day split into feedings every 1 to 2 hours and then gradually be increased depending on concurrent illness and estimated energy requirements. The GIT should be monitored for signs of tolerance to enteral nutrition.

In orphaned foals or where mare's milk is not available due to maternal illness or lack of production, mare's milk replacer may be used. These commercial products can be used effectively, but usually have higher ash and sodium content, which can result in intolerance (diarrhea, hypernatremia). Our hospital dilutes milk replacer with water by 25 to 30% over the recommendations to prevent adverse effects and improve tolerance to milk replacer. Information on the glycemic and endocrine responses to milk replacer versus mare's milk is lacking.

Glycemic monitoring

Limited energy reserves, sepsis, endocrine dysregulation, and decreased nutritional intake frequently combine to cause hypoglycemia in critically ill foals, requiring frequent monitoring of glycemia. Blood glucose concentrations should be measured at presentation, particularly in foals with weakness, altered mentation, seizure activity, or recumbency or where sepsis is suspected. Point of care glucose monitoring with validated glucometers is recommended after initial resuscitation and every 4 hours in foals undergoing intensive care. More frequent monitoring may be necessary for foals with severe disease or obtundation, with persistent hypoglycemia, or after changes in parenteral nutrition. Point of care glucometers validated for use in foals are recommended when frequent monitoring is necessary.[68,69] Continuous glucose monitoring systems were validated in both healthy and sick foals.[70]

Parenteral nutrition

Parenteral nutrition (PN) is necessary in sick foals that do not tolerate enteral feeding, foals with gastrointestinal disturbances (diarrhea, colic), or in foals with severe disease, causing alterations in mentation where enteral feeding is not feasible or carries risks of aspiration. There are commercially available PN products that contain dextrose and amino acid solutions and lipid emulsions, in addition to multivitamin and electrolyte supplementation (e.g., Clinimix E; Baxter Healthcare Solutions, Deerfield, IL).

The simplest form of partial parenteral nutrition (PPN) is a dextrose solution that can be administered alongside or within intravenous fluids. Most critically ill foals require intravenous dextrose to support minimal nutritional needs to prevent catabolism and to transiently provide energy for recovery. Fifty percent dextrose solutions contain 500 g/L of dextrose, and each gram of dextrose provides 3.4 kcal of energy.[13] Providing 4 to 8 mg/kg/min of dextrose mimics the energy supply to the fetus in the immediate neonatal period.[71] As already mentioned, RER in sick foals has been estimated to be around 50 kcal/kg/day.[65] Initiating PN at 25% of the foal's RER and increasing gradually while monitoring for hyper- or hypoglycemia is recommended. Intravenous dextrose solutions should be diluted to at least 10% due to hypertonicity. Dextrose solutions are unlikely to meet the foal's full RER but can be a temporary and low-cost option during resuscitation or while transitioning to enteral feeding.[13] Dextrose solutions between 2.5 and 10% are commonly used in equine hospitals for this purpose. They provide 85 to 340 kcal/L. If the transition to enteral nutrition will require more than 24 to 48 hours, the addition of amino acid solutions and/or lipid emulsions is recommended to provide additional calories and meet other nutritional needs.[13]

When adding protein to PN solutions, providing it at 4 to 6 g per 100 kcal is appropriate for most foals.[13] Commercial amino acid solutions are available ranging from 2.75 to 8%, and these solutions combined with 5 to 20% dextrose solutions are available for PPN. Amino acids provide 4 kcal/g of energy in the form of protein. The addition of lipid emulsions increases the energy density of PN solutions (lipids are calorie dense; 9 kcal/g) but also increases cost, risk of destabilization, and is contraindicated in foals with hyperlipemia or fatty liver. These metabolic derangements are common in neonates with sepsis or SIRS. Therefore, triglyceride concentrations should be measured regularly (every 24 to 48 hours) in neonates on PN or with severe disease. Lipids are available in 10 or 20% emulsions and, when added, can provide 30 to 60% of the nonprotein calories. There is conflicting literature on the addition of lipids to PN and an increased risk of complications in neonatal foals.[72,73] Most of these complications are likely related to the severity of the primary disease. The addition of lipids is likely to be beneficial in patients when long-term PN is necessary or in patients with persistent hyperglycemia.[74] The addition of lipids to PN is becoming more routine.

Complications of PN include hyperglycemia, which, if persistent, may require insulin therapy, as well as thrombophlebitis and hyperlipemia.[72] Parenteral nutrition in the absence of enteral feeding may lead to adverse effects on GIT maturation and integrity,[66,67] although this has not been studied in horses or foals. Trophic feedings, in which very small amounts of milk are administered via nasogastric tube (10 to 25 ml per feeding), may be administered to attempt to maintain enterocyte health, while minimizing adverse effects of enteral nutrition in foals that are intolerant. However, the validity of this practice is unknown. Hypokalemia, hypomagnesemia, and hypophosphatemia can occur with PN due to increases in glucose and insulin causing intracellular shifts in these electrolytes. Intravenous supplementation of these electrolytes should be considered, and their concentrations should be monitored every 12 to 24 hours in critically ill patients on PN. Due to the increased risk of infection and contamination of glucose-containing solutions, they should be prepared and mixed aseptically, minimizing opportunities for contamination (i.e. reducing the frequency of puncturing fluid bags for additives, limiting detaching/reattaching fluid lines to the patient).

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Insulin administration

Critically ill foals often develop hypoglycemia due to energy deprivation, minimal energy reserves, bacteremia, systemic inflammation, or endocrine dysregulation. In foals under a negative energy balance or hypoglycemia, low insulin, high glucagon, and high triglyceride concentrations indicate a proper homeostatic response to restore energy balance.[32] Failure of these mechanisms could be detrimental. Hyperglycemia is observed less frequently. In hospitalized foals with persistent hyperglycemia (glucose concentrations elevated for hours with minimal to no energy supplementation), reduced insulin secretion rather than insulin resistance should be suspected.[32,34] Insulin resistance, characterized by normo- or hyperglycemia with hyperinsulinemia, occurs in critically ill foals, although is uncommon.[35] Most septic foals have low insulin concentrations.[32,34,35] In persistently hyperglycemic foals, insulin replacement therapy to restore normoglycemia should be considered. Clinicians must be careful with insulin administration to sick newborn foals because most are insulin sensitive and may develop hypoglycemia.[24] It is better to use continuous rate infusions (CRI) over intravenous or subcutaneous administration, except in those with severe hyperglycemia. The recommended starting CRI for regular insulin is 0.0025 to 0.01 IU/kg/h with steady increases every 2 to 4 h to 0.2 IU/kg/h, with even higher rates until normoglycemia is restored.[13,58,73,75,76] Lack of response to this approach is usually associated with a poor prognosis. It is important to monitor glucose concentrations closely to avoid hypoglycemia. When defining hyperglycemia, it is important to note that glucose concentrations of 200 to 250 mg/dL in healthy foals after nursing are normal.[24,31] However, these glucose values are abnormal in foals receiving parenteral dextrose or parenteral nutrition. In these animals, hyperglycemia results from endocrine dysregulation or organ dysfunction or is iatrogenic. Before using insulin, adjusting caloric rates should be considered. Similarly, evaluation of the metabolic status and electrolytes is important. Ions such as potassium, phosphorus, and magnesium are intricately related to glucose dynamics. Incretin analogs are used in human and small animal medicine to increase insulin secretion to restore normoglycemia but have not been evaluated in foals.

Conclusion

Energy homeostasis during the transition from late gestation to the neonatal period requires complex interactions of multiple endocrine systems, preventing hypoglycemia and energy dysregulation. Investigation in this field is ongoing, and current evidence suggests profound differences between horses and foals in endocrine responses and nutritional requirements. Critical illness in newborn foals is common, creating diagnostic and therapeutic challenges for clinicians. Recent information provides insights on the pathophysiology of energy dysregulation, raising the importance of an intact GIT to better regulate energy.

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Appendix 1

Example calculation for a 50-kg foal
Enteral nutrition was as follows:
Resting energy requirement (RER) for a critically ill foal was 50 kcal/kg/day[65]

$$50\ \text{kcal} \times 50\ \text{kg} = 2{,}500\ \frac{\text{kcal}}{\text{day}}$$

Mare's milk is estimated to contain ~0.5 kcal/ml (Oftedal et al)[61]; therefore:

$$\frac{2{,}500\ \text{kcal/day}}{0.5\ \text{kcal/mL milk}} = 5{,}000\ \text{mL/day or 5 L/day milk}$$

This can also be estimated at roughly 10% of the foal's body weight in kilograms:

$$\frac{50\ \text{kg} \times 10\%}{100} = 5\ \text{kg} + \sim 5\ \frac{\text{L}}{\text{day}}$$

$$\frac{5{,}000\ \text{mL}}{12\ \text{feedings per day}} = 417\ \text{mL per feeding (q 2 h)}$$

Feedings can gradually increase as the foal's condition improves (up to 20 to 25% of body weight per day).
Parenteral nutrition was as follows:

$$\text{RER} = 50\ \text{kcal/kg/day}$$

$$50\ \text{kcal} \times 50\ \text{kg} = 2{,}500\ \frac{\text{kcal}}{\text{day}}$$

Four to 6 g protein per 100 kcal can be provided by a 20% dextrose and 5% amino acid solution:

$$20\%\ \text{dextrose} = 0.2\ \text{g/mL} \times 3.4\ \text{kcal/mL} = 0.68\ \text{kcal/mL}$$

$$5\%\ \text{amino acid} + 0.05\ \text{g protein/100 mL} = 0.05\ \text{g/mL}$$
$$\times\ 4\ \text{kcal/mL} = 0.2\ \text{kcal/mL}$$

[5% amino acid and 20% dextrose solution provides ~ 5 g/100 kcal; 5 g/100 mL]

Kcal from dextrose was 0.68 kcal/ml.
Kcal from protein was 0.2 kcal/ml.

$$0.68\ \frac{\text{kcal}}{\text{mL}} + 0.2\ \frac{\text{kcal}}{\text{mL}} = 0.88\ \frac{\text{kcal}}{\text{mL}}$$

$$\frac{2{,}500\ \text{kcal/day}}{0.88\ \text{kcal/mL}} = \frac{2{,}841\ \text{mL/day}}{24\ \text{h}} = 118\ \text{mL/h}$$

Begin at 25% of RER and gradually increase every 4 to 6 hours while monitoring for hyperglycemia.

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