How to Interpret Common Hematologic and Serum Biochemistry Differences Between Neonatal Foals and Mature Horses

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There are important and significant differences in normal hematologic and serum biochemical parameters between neonatal foals and mature horses. Failure to recognize these differences can lead to erroneous interpretation of neonatal clinical pathologic values. Author's address: Department of Large Animal Medicine, H-302 College of Veterinary Medicine, University of Georgia, Athens, GA 30602; e-mail: bartonmh@uga.edu.

1. Introduction

The dynamic physiologic changes and unique diet during the neonatal period contribute to distinctive features in clinical pathologic parameters of healthy foals relative to healthy adult horses. When reporting results, most diagnostic laboratories only provide reference ranges for mature horses. Thus failure to recognize the unique differences that occur in foals relative to adult horses can lead to erroneous interpretation of neonatal clinical pathologic values. Methodology can also profoundly affect the values reported in a reference range, which can lead to erroneous interpretation when extrapolating results between laboratories. Ideally, normal reference ranges for foals should be established within each diagnostic laboratory. However, funding limitations typically preclude provision of this data. Thus, the main objective of this session is to review distinct features of common hematologic and serum biochemistry parameters in foals relative to mature horses.

2. Materials and Methods

Medline, Pubmed, Agricola, and CAB databases were reviewed. Inclusion in this review was based on clinical applicability. To avoid unnecessary duplication, common themes in difference or trends of differences were extracted for this review. Given that methodology can influence the reported value or range of values, reference to absolute values will be limited. When applicable, breed differences will be noted.

3. Results

Hematology

Red Blood Cell Parameters

Red blood cell parameters are highly dynamic during the neonatal period. In general, immediately after birth, the red blood cell (RBC) count, hemoglobin (Hgb) concentration, packed cell volume (PCV), and hemocrit (Hct) are similar to slightly greater than adult horses.[1–4] However, in most breeds, within 48 hours, these values decrease and continue to decrease to the low end or below the reference range for mature horses.[5] For example, it is not atypical for the PCV to decrease in the first 48 hours of life from values of approximately 45 to 50% at

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birth to 35 to 40%, whereas absolute RBC counts do not decrease as dramatically.[1–4] The higher PCV at birth likely represents terminal placental transfer of blood and the physiologic stress of parturition inducing splenic contraction. The initial rapid reduction in PCV is due to a combination of adaptation to extrauterine life and hemodilution from blood volume expansion after ingestion of colostrum. The PCV, Hct, and Hgb continue to gradually decrease through the first month of life, most often with values falling in the low-normal adult range or sometimes, slightly below the adult range.[1–4] The absolute RBC count often stays within the normal adult range; thus, the decrease in PCV is mostly due to the fact that neonatal erythrocytes become smaller (i.e., microcytes) and remain relatively uniform in size compared with adult RBCs. This is reflected in the mean corpuscular volume (MCV) values, which are similar to adult values at birth, and then gradually decrease, reaching a nadir between 3 and 5 months that is below the adult range.[5] The MCV can remain lower than adults for up to a year.[1] Mean corpuscular hemoglobin concentration (MCHC) is derived by diving the Hgb concentration by the Hct and is more accurate than the mean corpuscular hemoglobin (MCH). In foals, the mean corpuscular hemoglobin concentration tends to be slightly lower to within normal limits relative to adults. Thus, collectively and compared with adults, foals often seem to be mildly anemic with smaller RBCs with less hemoglobin. This physiologic anemia is common and seems to be due to reduced stimulus for erythrogenesis and decreased iron availability.[2,6] Hypoxemia is a strong stimulus for erythropoiesis. After birth, foal RBCs have greater amounts of 2,3-diphosphoglycerate, which typically occurs with immature RBCs.[6] 2,3-diphosphoglycerate facilitates the release of oxygen delivery to tissue; thus, greater concentrations in the neonate may curtail erythrogenesis. Serum iron and ferritin concentrations decrease rapidly in the first few days and total iron-binding capacity is greater in the neonatal foal than the adult and may be due in part to the low iron content of milk versus colostrum and depletion of fetal iron stores.[5,6] The concurrent presence of microcytes is supportive evidence for functional iron deficiency. Relative lack of iron availability and the physiologic anemia associated with it rarely result in clinical abnormalities in the neonatal period. However, it would be atypical for the PCV to decrease below 20% in a foal or to decrease rapidly, in which case additional diagnostics would be warranted. In light of the fact that foals have functional iron deficiency, they may be more prone than adult horses to the development of iron deficiency anemia, especially if concurrent disease is present.[7]

It should be noted that breed differences have been noted particularly in RBC indices in horses. Although there have not been direct breed comparisons within the same laboratory setting, comparisons between studies suggest that physiologic anemia and the changes in RBC indices may be less dramatic in draft breeds compared with light-breed horses.[3] In one study, the degree of anemia in Arabian foals during the first year of life was more pronounced than in Thoroughbred or Quarter Horse foals.[8] Donkey foals follow the same trend as light breed foals.[4,9]

Leukogram

Total leukocyte and absolute neutrophil counts tend to be the same or slightly exceed adult values whereas lymphocyte counts tend to be the same or below mature horse reference ranges during the first day of life. During the first few days, absolute lymphocyte counts may fall below 1000/μL. The higher neutrophil-to-lymphocyte ratio may be due in part to the endogenous release of cortisol at parturition. In fact, lack of the parturition cortisol surge in otherwise-healthy premature foals is typically accompanied by characteristic neutropenia at birth, wherein the severity of the neutropenia correlates with the likelihood of survival.[10] Lymphocyte counts can remain at or below the lower end of the adult reference range for the first few months of life. However, foals are also more likely to experience stress when handled for venipuncture and physiologic lymphocytosis subsequent to catecholamine release can result in a rapid increase in the total lymphocyte count. Band neutrophils are expected to remain less than 250/μL during the neonatal period. Eosinophils are typically absent.

Coagulation

Coagulopathy is common in critically ill neonates with one recent study reporting at least one abnormal coagulation parameter in 64% of foals with septic shock.[11] Standard testing of the coagulation system would include determining the platelet count; prothrombin and activated partial thromboplasin times; fibrinogen concentration; fibrin degradation products or d-dimer concentration; and perhaps, antithrombin activity. As for many clinical pathologic parameters, methodology can directly affect the absolute values determined, and this is particularly true for coagulation testing. Platelet counts are most accurate if the blood is collected into sodium citrate as the anticoagulant. Platelet counts are the same or slightly greater in foals during the first few days of life and then comparable with adult values.[12,13] Likewise, the prothrombin and activated partial thromboplasin times are the same or longer and fibrinogen concentrations are lower than the adult horse in the first few days of life.[11–13] Fibrin degradation products concentrations are significantly greater than adult horses for at least 2 weeks.[12,13] Antithrombin activity is significantly lower during the first month of life, with mean values approximately one half adult values at birth.[12,13]

Serum Biochemistry

Proteins

The total serum protein concentration varies considerably in the first 24 to 36 hours, depending on timing of absorption of colostral immunoglobulin. Presuckle total serum protein concentration is usually less than 5 g/dL and thus would fall below the normal adult reference range. Post-suckle total serum protein concentrations usually are greater than 6 g/dL, but may remain in the low to slightly below the normal adult reference range for several weeks. Albumin concentrations tend to stay within the same reference range as adult horses, thus the albumin-to-globulin ratio is usually normal or slightly lower than adult horses.[14] Although absolute total serum protein concentration is not a reliable indicator of transfer of passive immunity, a low albumin-to-globulin ratio may be supportive evidence for partial or complete failure of passive transfer[14] and should be verified by a more specific test for immunoglobulin concentration.

Electrolytes

The only subtle difference in sodium concentration in foals relative to adult horses is that the serum sodium concentration might be at the lowest end of the normal adult reference range in the first 24 to 48 hours. This most likely is due to mild hemodilution following osmotic fluid expansion after absorption of colostral immunoglobulin. Otherwise, serum sodium, potassium, chloride, bicarbonate, magnesium, and calcium values typically remain stable during the neonatal period with no significant differences relative to the mature adult horse.[15] Serum inorganic phosphorus concentration is similar to adult values at birth, and then gradually increases over the first 2 months and may be slightly greater than adult values during the first year of life.[14] For example, adult serum phosphorus values usually are less than 4 mg/dL, whereas foal serum phosphorus concentrations can range between 6 and 8 mg/dL in the first year of life.

Renal

Serum creatinine values are often greater than adult values in the first 24 to 36 hours of life with values of 4 to 5 mg/dL, and as high as 27 mg/dL, without concurrent evidence of renal dysfunction.[14,16] Endogenous serum creatinine is removed from fetal circulation via the placental circulation. Thus, higher creatinine values in the first day of life more likely reflect placental dysfunction rather than reflect primary renal disease. Furthermore, foals usually do not urinate until they are between 6 and 12 hours old, which also delays the clearance of endogenous creatinine. Spurious hypercreatininemia is commonly reported in foals with neonatal encephalopathy.[16] However, foals with spurious hypercreatininemia without renal disease typically have normal concurrent blood urea nitrogen concentrations, and the serum creatinine concentration usually steadily decreases to normal values within the first 72 hours of life.[16] Creatinine concentrations frequently fall below 1.0 mg/dL in the well-hydrated and vigorously nursing foal. Blood urea nitrogen values are equivalent to adult values at birth and then tend to drop below the lowest end of normal adult range (12 mg/dL) from the first few days of life to 5 months of age.[14]

Hepatic

The liver serves many diverse roles in normal homeostasis including protein, lipid, and carbohydrate metabolism, vitamin storage, hematopoiesis, detoxification, and excretion. Total bilirubin concentration, primarily consisting of unconjugated or indirect acting bilirubin is significantly greater in neonatal foals than mature horses, peaking in the first week (up to 5 mg/dL) and remaining increased during the first 2 weeks of life.[14,17,18] Unconjugated bilirubin values are often two to four times the adult mean value during this time. Physiologic hyperbilirubinemia of neonates is primarily caused by reduced availability of bilirubin-binding protein that is responsible for hepatocellular uptake of bilirubin and can be further exacerbated by anorexia. Physiologic hyperbilirubinemia, coupled with physiologic anemia during this period can be misconstrued as evidence of hemolytic anemia. Bilirubin concentrations in donkey foals tend not to be as high as horse foals and often are within adult donkey reference range.[9,19]

Foals have less stored hepatic glycogen than adult horses and are not yet hindgut fermenters. Thus glucose concentrations tend to be highly variable, depending on demand, stress, and nursing frequency. In general, glucose concentrations are usually greater than the normal adult values during the first month of life, often exceeding twice the adult upper range of values. Likewise, serum triglycerides are highly variable and reflective of nursing. Values may be as high as 340 mg/dL in healthy foals in the first few months of life, when adult values rarely exceed 50 mg/dL.[14,17,18]

In general, liver-associated enzymes are greater in neonatal foals and have larger standard deviations from the mean compared with adults.[18,20] The liver-specific enzymes sorbitol dehydrogenase and gamma glutamyltransferase (GGT) are either unaffected or slightly increased in the first 2 weeks and increased between 1 and 4 weeks of life, respectively.[17,18,20] Unlike ruminant neonates, there is little GGT in colostrum and thus, GGT levels do not correlate with transfer of passive immunity in foals. Alkaline phosphatase (ALP) activity is very high the first week of life (up to 3000 U/L) and remains two to four times the adult mean range (64 to 214 U/L) for the first year of life.[14,17,21] The relatively higher ALP activity of neonatal foals is primarily due to the bone isoenzyme[21] and increased release associated

Table 1. Common Unique Differences in Equine Neonatal Clinical Pathologic Parameters Relative to Adult Horses

Parameter	Interpretation Relative to Adult Reference Ranges
Packed cell volume	Lower for first few months
Mean corpuscular volume and mean corpuscular hemoglobin concentration	Lower for first few months
White blood cells	Variable, but tend to be the same or slightly greater. Lymphopenia or lymphocytosis is not uncommon.
Prothrombin and activated partial thromboplastin times	Same or longer for first few days
Fibrinogen concentration	Lower for first few days
Fibrin degradation products concentration	Greater for first two weeks
Total serum protein concentration	Lower for four to six weeks
Serum globulin concentration	Lower for four to six weeks
Creatinine concentration	May be greater for first 48 hours, then drop below adult values
Blood urea nitrogen concentration	Initially the same at birth, but may drop below adult values during first few months
Glucose concentration	Same or greater during first month
Triglyceride concentration	Same or greater during first several months
Total bilirubin and unconjugated bilirubin concentrations	Greater during the first 2 weeks of life
Gamma glutamyltransferase activity	May be slightly greater for first 2 weeks
Alkaline phosphatase activity	Greater during first year
Serum bile acids concentration	Greater during first 6 weeks
Phosphorus concentration	Greater during the first year
Creatinine phosphokinase activity	May be lower during the first year
T_3 and T_4 concentrations	Greater than adults for first year
Cortisol concentrations	Initially greater at birth, then often falling below the adult mean during the first few weeks

with osteoblastic activity during rapid bone growth and bone stress.

Bile acids concentration is frequently used as a functional assay of the liver.[18] Bile acids concentrations are significantly greater than mean adult values during the first 6 weeks of life, with radioimmunoassay values exceeding enzymatically determined values.[18] Increased serum bile acids concentration in the neonatal period may be due to upregulation of hepatic production, reduced excretion into the bile, unique intestinal floral effects on the bile-acid composition of the neonate, or enhanced intestinal absorption or uptake from the portal circulation.

Collectively, greater bilirubin and serum bile acids concentrations and greater serum GGT, sorbitol dehydrogenase, and ALP activities in the neonatal period, could erroneously lead to a diagnosis of liver disease.

Muscle Enzymes

Aspartate aminotransferase (AST) activity is primarily associated with muscle, although some AST activity is also found in the liver. In foals, AST activity tends to be the same or slightly lower than adult values during the first week of life, but values tend to remain within adult reference ranges as they continue to exercise and grow.[14,20] Creatine phosphokinase activity is fairly comparable with adult ranges, although variation in foals' normal ranges may dip below adult values in the first few months.[14] Increased creatine phosphokinase activity is reported in 62% of foals with neonatal encephalopathy.[22]

Endocrine

At birth and during the first few days of life, thyroid hormones (T_3 and T_4) are at least ten times (991 ng/dL and 29 μg/dL) greater than adult horse values. Both T_3 and T_4 values gradually decrease, approximating adults values by 2 weeks (T_4) to 1 month of age (T_3), although values may remain two times greater than adult values for the first year of life.[23–25]

A cortisol surge in response to adrenocorticotropic hormone is an important physiologic event at parturition in both the mare and foal. Adrenocorticotropic hormone concentrations are greatest at birth (up to 968 pg/mL),[26,27] rapidly decreasing within hours to approximate adult values within 48 hours. Likewise, cortisol concentrations are also highest in the first 30 minutes after birth (6 to 13 μg/dL), but drop within 48 hours, often falling below mean adult horse values during the first few weeks of life.[26,27] Premature foals have significantly higher adrenocorticotropic hormone and lower cortisol concentrations at birth (often < 1 μg/dL) than full-term foals, indicating dysfunction of the hypothalamic-pituitary-adrenal axis.[10]

4. Discussion

Relative to adult horses, there are several unique features of neonatal clinical pathologic parameters that must be considered for accurate interpretation.

Failure to recognize these differences can lead to erroneous interpretation. Ideally, age-related normal values should be used from the laboratory performing the analyses for accurate interpretation. If age-specific reference data is not available for neonatal foals, some generalizations can be applied relative to adult reference values and are summarized in Table 1.

Acknowledgments

Declaration of Ethics

The Author declares that she has adhered to the Principles of Veterinary Medical Ethics of the AVMA.

Conflict of Interest

The Author declares no conflicts of interest.

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