

NEONATAL PHYSIOLOGY

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Neonates are not miniature adults. Their physiology is unpredictably different from adults. The neonatal period is the physiologic transition period from the aquatic, self-contained fetal life with its full dependence on maternal nutrition, waste handling and environmental homeostasis to independent extrauterine life where birth and breaking the umbilical cord literally means the neonate must adapt its physiology to provide all the necessities of independent life. The term "neonate" is derived from the Latin natus (to be born) and refers to a newborn during the first weeks of life during the physiologic transition. Although strictly speaking it should encompass the entire period until the transition is complete for all organ systems, by convenience it is usually defined as the first 3 to 4 weeks of life in most domestic species.

The physiology of the fetus is much different in very many aspects than the physiology of the adult. At times the fetal physiology seems counterintuitive to those familiar with adult physiology. For instance we understand the logic of the adult kidney producing concentrated urine in response to hypovolemia as it will help maintain vascular volume. But when the fetus produces concentrated urine which may increase the osmolarity of the fetal fluids it may not only tend to prevent reabsorption of the fluids, it may actually draw more fluid from the fetus into this fluid reserve leading to a negative effect on volemia. On the other hand when the fetus produces dilute urine the resulting decrease in fetal fluid osmolarity tends to enhance reabsorption of fetal fluids by the fetus having a positive effect on volemia.¹ Another example is the fetal heart rate response to hypoxemia. In the adult, hypoxemia stimulates tachypnea and tachycardia as the physiology adjusts in an attempt to deliver more oxygen to tissues. But in the fetus hypoxemia results in bradycardia. This bradycardia is a logical adaptation to hypoxemia. Unlike the adult who can bring more oxygen in contact with blood by increasing its minute ventilation, the fetus has no way to communicate to the mother that it needs an increase in maternal placental perfusion. The fetus meets this challenge by maximizing perfusion of fetal placenta and by increasing vascular tone directing blood flow to vital organs. But this increase in afterload will increase cardiac work and thus oxygen demand. By slowing its rate the heart adapts to the new circulatory pattern but simultaneously requires no more oxygen than it required before the hypoxemia. Although these examples are of fetal physiology, the neonate has a strong memory of fetal physiology. Disease states may slow the transition to pediatric physiology and even when the neonate has made a complete transition, with stress, the neonate may revert to the more familiar fetal physiology. These examples emphasize the importance of understanding fetal and neonatal physiology to appreciate the neonate's response to disease and more importantly to predict its response to our therapeutic interventions.

My clinical experience is with foals, calves, kids, lambs and crias which has allowed me to temper information from experimental studies in these species and comparative information from studies in other species, emphasizing what is clinically relevant. But as I have no clinical experience with puppies or kittens I submit the following ideas for your consideration. Some of the ideas presented here may have little clinical relevance. It should also be fully understood that although superficially it appears that the organ systems have similar maturational patterns between species with the major difference being when in that maturational process the fetus is born, the unpredictable impact of interspecies differences on organ development and maturational processes makes extrapolation of data obtained in one animal species describing fetal and neonatal physiology responses to other animal species error prone.

Fluid Physiology

Fluid dynamics in the fetus and neonate is much different than that of the adult and these differences have significant implications in responses to fluid therapy. These differences are due to unique characteristics of the interstitium, lymph flow and endothelial permeability. The interstitium is a heterogeneous space which dynamically controls its fluid content much like the vascular space but by poorly understood mechanisms. The interstitial space of the fetus and neonate is easily expanded relative to that of the adult with compliance in the ovine fetus roughly 10 times that observed in the adult. The volume of fluid within the lymphatic system is surprisingly small and averages only 1 mL/kg body weight in adult dogs and may be similar in the fetus and neonate. In fetal sheep, thoracic duct lymph flow averages 0.25 mL/minute/kg which is substantially higher (about 5x) than those in the adult. As with most physiologic phenomena the neonate appears to fall between these 2 extremes. The lymph flow from subcutaneous tissue in anesthetized puppies is approximately twice that observed in adult dogs per kg body weight. Furthermore, lymph flow from the lungs is higher in anesthetized newborn lambs and puppies than in adults. The local, as well as whole body lymph flow rates are significantly greater in the neonatal period than later in life. The increased lymphatic flow during the neonatal period is probably indicative of the elevated interstitial volume in the neonate in relation to the adult and the higher capillary permeability. The capillary filtration rate of fluid in fetal lambs is approximately 5x that of the adult

and the filtration rate for proteins about 15x higher. This increased filtration rate has been thought to be primarily due to poor precapillary tone resulting in higher capillary hydrostatic pressure. The role of the glycocalyx, the major endothelial barrier, has not been investigated. The neonate, depending on the maturity at birth, may have very similar endothelial filtration characteristics in many vascular beds.^{1,2}

During the last few days of gestation fetal blood pressure increases significantly (by 20% in fetal lambs) although fetal blood pressures are still much lower than adult blood pressure. Part of this increase in blood pressure is thought to be transmitted to the capillaries because of poor precapillary tone resulting in increased transcapillary filtration of fluid and protein. Further increases in blood pressure during labor and birth is thought to result in a decrease in plasma and blood volume (18% and 12% respectively in fetal sheep) resulting in an increased hematocrit secondary to these fluid shifts. Other reasons for the fluid shift include direct compression or transformational change of the fetus leading to increased venous pressure and increases in vasoactive hormones including arginine vasopressin, norepinephrine, cortisol, and atrial natriuretic factor.¹

As the result of these fluid shifts drawing from the fetal fluids or maternal circulation and accumulating in the fetal interstitium all neonates are born fluid overloaded to one degree or another. In the normal neonate the rate of loss of this fluid varies. Foals hold on to this extra fluid and slowly lose it over weeks. Many other species may lose 10-15% of their body weight in the first days after birth. It is important to recognize this fluid loss for what it is and not try to replace it with more fluid as persistent fluid overload is now recognized as a major contributor to poor outcomes.¹

There are considerable differences in the ratio of interstitial volume to plasma volumes in the newborns of different species. For example 1 to 3 week old lambs have an interstitial to plasma volume ratio of 5.2:1 whereas newborn puppies have an interstitial to plasma volume ratio of 2.1:1. The hematocrit at birth loosely correlates with this ratio; the higher the hematocrit, the higher the ratio.¹

Consequences of Neonatal Fluid Physiology

Response to Hemorrhage: Perinatal blood loss of the fetus or neonate can occur after rupture of umbilical vessels, during premature placental separation, by bleeding of the fetus into the maternal circulation (fetomaternal transfusion) or into a twin fetus (fetofetal transfusion), or by internal bleeding, for example, long bone fractures or intestinal hemorrhage secondary to necrotizing enterocolitis. In adult dogs, cats, and sheep, 24 to 48 hours is required for blood volume to return to normal after a 30% loss of blood. This restoration of volume occurs as plasma volume returns to or rises above normal, whereas RBC volume remains reduced. The time required for full volume restoration after hemorrhage in the fetus or neonate is shorter than in the adult. Fetal sheep restore twice the volume than adults within 30 minutes after rapid hemorrhage. The ovine fetus restores its blood volume to normal within 3 to 4 hours after a 30% hemorrhage which is in one tenth the time required in the adult. This rapid restoration is mediated by a translocation of fluid and protein from the interstitial space into the vascular space. Neonatal kittens and rabbits are also better able to tolerate blood loss than adults, as more blood per kg must be removed before arterial pressure decrease. This was attributed to a more rapid mobilization of interstitial fluid in the young animals in the first week of life. Neonatal lambs also rapidly restore their blood volume to normal after hemorrhage.¹

Responses to Volume Loading: Rapid intravascular infusions of isotonic solutions expand plasma volume of fetal lambs by only 6 to 7% of the infused volume after 30 to 60 minutes because of rapid transfer of the infused fluid into the interstitial spaces. When adults receive IV fluids average intravascular retention is 20% to 50% of the infused volumes after 30 to 60 minutes. The poor intravascular retention of crystalloid during fetal life and the early neonatal period is due to the high interstitial compliance and the high capillary filtration coefficient which permits very rapid fluid shifts.^{1,3}

Once fluid overloaded the neonate retains the fluid much longer than the adult which is thought to be largely because of the reduced intravascular retention of fluid in the neonate. After volume loading, normal adults (dogs, sheep) will excrete the entire volume load through their kidneys over a period of several hours as plasma renin activity and plasma concentrations of arginine vasopressin and atrial natriuretic factor all change in a direction appropriate for elevating urine flow. Puppies and lambs and likely other neonates will retain the same fluid load for 24 to 36 hours probably because the volume load escapes the intravascular before plasma volume sensors can recruit these hormones to exert their diuretic response. Thus the neonatal urine flow rapidly returns to normal after rapid vascular volume expansion.¹

Both fetal and newborn sheep undergo an increase in left thoracic duct lymph flow up to 3.5 times normal after vascular volume expansion augmented by angiotensin II. Because of the dynamics of this increased lymph flow even small increases in central venous pressure as will occur in response to rapid administration of intravenous fluids will result in a dramatic decrease in the lymphatic flow rate making the neonate receiving intravenous fluid therapy particularly susceptible to the development of edema.¹

Responses to Hypoxia: Hypoxia in the fetal lamb results in elevation of capillary pressure within the fetal body. There are no changes in fetal arterial or venous pressure if the hypoxia is mild because of vasodilation in selected organs but if the hypoxia is moderate to severe there will be an increase in arterial and venous pressures. This change in capillary pressure due to hypoxia will result in a greater transfer of fluids into the interstitial space leading to increased fluid overload. So although all neonates at birth and just after are fluid overloaded, the fetus or neonate suffering from hypoxia/asphyxia has a greater degree of fluid overload often resulting in the somewhat unique situation of having a hypovolemic individual who is fluid overloaded.¹

Renal Physiology

There is marked variation in the degree of renal maturation at birth between species.⁴ In normal lambs, foals and calves nephrogenesis is complete by birth and GFR reaches adult levels in days. In the dog nephrogenesis continues for at least 2 weeks after birth.⁵⁻⁶ There is a paucity of information regarding nephrogenesis in the cat and kid.⁶ The canine neonatal kidney is functionally characterized by a low glomerular filtration rate (GFR), renal plasma flow (RPF), filtration fraction (FF), altered para-aminohippurate (PAH) handling, depressed reabsorption of amino acids and phosphate, exaggerated proximal tubule natriuresis, and low concentrating ability.^{5,7-10} In puppies serum creatinine levels and BUN concentrations are lower than in the adult dogs. Foals, calves, lambs, kids and crias also have BUN levels lower than adults and these levels stay low as long as the neonate has a positive energy balance. Creatinine levels in foals, calves, kids and crias is much higher than adult levels at birth. If the neonate is normal these levels will decrease to below adult levels (generally below 1.1 mg/dl and as low as 0.4 mg/dl depending on the species) within 48 hours of birth. If there has been fetal distress the birth creatinine levels in these species at birth may be as high as 20-30 times normal. This increase is not a reflection of renal disease but rather an indication of fluid shifts from the creatinine rich fetal fluids to the neonate as outlined above in the section on fluid physiology (the fetal foal's allantoic fluid Cr is 120-160 mg/dl and anionic fluid Cr 8 to 12 mg/dl). Serum phosphorous concentrations are typically increased in neonates because of special renal handling of that ion.¹¹

In general in all species fetal and early neonatal arterial blood pressure is lower than that of adults but this is balanced by lower vascular resistance insuring perfusion. In the fetus about 3-5% of cardiac output perfuses the kidneys. At birth this percentage rapidly increases to 15% due to a modest increase in arterial pressure and although renal vascular resistance also increases it does so to a lesser extent relative to other vascular beds resulting in the kidneys capturing a greater percent of cardiac output. The speed in which the arterial pressure and vascular resistance reach adult levels vary between species and is closely associated with changes in the baroreceptor response and set point and autonomic maturation. The range of blood pressure within which renal blood flow is maintained in the immature kidney is the normal range for that age. The "autoregulatory range" increases as blood pressure increases to adulthood levels.¹³ In puppies the GFR and RPF increase in parallel with arterial pressure and relative decreased in vascular resistance. In the foal, calf and lamb the GRF becomes adult-like independent of the increase in blood pressure. In puppies renal blood flow is directly correlated with arterial pressure and does not seem to be altered by inhibition of angiotensin until approximately 6 weeks of age.⁶ The balancing of perfusing blood pressure and vascular resistance is vital for proper renal function during the neonatal period. At least in large animal clinical neonatology the most common cause of renal dysfunction is Neonatal Vasogenic Nephropathy where this balance is not maintained because of abnormal levels of vasoactive substances and sympathetic tone. Prostaglandins are vital in counterbalancing endogenous vasoconstrictors by promoting afferent arteriolar vasodilation. Unlike the adult, high prostaglandin activity is physiologically necessary to maintain sufficient perfusion of the newborn kidney. Nonsteroidal anti-inflammatory drug therapy has a much greater potential for producing renal toxicity in neonates than in adults. They reduce GFR and RBF so are associated with Neonatal Vasogenic Nephropathy, oliguria and fluid overload. Both nonselective and selective cyclooxygenase inhibitors likely share the same adverse effect and their use is not advised in the neonate.⁶ Other major differences in the neonate's response to vasoactive agents from adults is beyond the scope of this talk. It is interesting to note that in the neonatal rabbit, decreases in body temperature as little as 2 C are able to induce renal vasoconstriction and decrease GFR.¹⁴ Hypothermic neonates are at risk. In normal neonates change in environmental temperature may play an important role in the sympathoexcitatory response seen at birth. This response occurs before a decrease in core temperature and is reversible with rewarming, suggesting it is mediated by sensory input from cutaneous cold-sensitive thermoreceptors rather than a response to a change in core temperature.

There is considerable variation in the number of nephrons in normal subjects, and there is a linear relationship between the number of glomeruli and birth weight at least in humans.² Despite a significant increase in glomerular volume, both normal and compensatory renal growth are primarily caused by an increase in proximal tubular mass. Intrauterine growth restriction can result in fewer nephrons than in normal neonates. The timing of intrauterine growth restriction may determine whether nephron numbers are reduced. Perinatal asphyxia or severe circulatory disturbances

can cause irreversible nephron loss. Exposure of the fetus to maternal administration of prostaglandin inhibitors, glucocorticoids, aminoglycosides, beta lactam antibiotics, or cyclosporine may impair nephrogenesis.

In general tubular function is poorly developed in most species at birth. Even in the species where GFR is normal just after birth, the tubules are short and the carrier density less than adult levels resulting in limited tubular function. In puppies the urine specific gravity is limited (1.006 to 1.017) and initially it is normal to find protein, glucose, and various amino acids in the urine. By 3 weeks of age, urine protein and glucose concentrations approach those of the adult dog, and urine concentration is expected to compare with that of the adult by 8 weeks in kittens and 12 weeks in puppies.^{6,15} In large animal neonates urine specific gravity has a broad range (1.001 to > 1.035) within 24 hours. On the usual milk diet the urine specific gravity is generally < 1.004 but in foals the first urine, which is delayed approximately 12 hours, usually has a urine specific gravity > 1.035. Although blood and protein may appear in urine during the first 48 hours of life generally the urinalysis is similar to the adult. Acid base control develops postnatally in all species.⁴

It is interesting to note that although fractional Na absorption in the proximal tubules is not fully developed at birth enhanced absorption in the distal tubule insures Na conservation allowing for the positive Na balance needed for growth despite the fact that a fresh milk diet contains very small amounts of Na. This is achieved by up-regulation of several Na carrier systems. For example in the face of a Na load total nephron fractional Na reabsorption was 0.91 for adult dogs and 0.98 for the puppy ($p < .01$). However, proximal tubule Na fractional reabsorption was greater in the adult dog (0.64) than in the puppy (0.48, $p < .01$), whereas distal nephron Na fractional reabsorption was much greater in the puppy (0.51) than in the adult dog (0.26, $p < .01$).¹⁶ The distal tubule handling of Na seems to be less responsive to Na loads, continuing maximum reabsorption in some neonates rapidly leading to Na overload. Because the neonatal kidney function predisposes to Na overload and the neonatal fluid physiology predispose to prolong fluid overload and (at least in puppies) there may be limited urine dilution, fluid therapy should be administered with great care.¹⁷ Sodium and fluid overload is a common iatrogenic problem in all neonatal species.

Cardiovascular System

At birth, the cardiovascular system changes dramatically with arterial blood pressure, heart rate, and cardiac output increasing, and blood flow distribution undergoing significant regional changes. Cardiac output in the newborn lamb is four times greater than in the adult.¹⁸ The neonate initially retains the fetal low-resistance-high-flow system.⁶ To maintain peripheral perfusion, the neonate must maintain a higher heart rate, cardiac output, plasma volume, and central venous pressure as compared with the adult. During the neonatal period, systolic blood pressure in puppies was noted to increase from 61 ± 5 mmHg at birth to 139 ± 4 mmHg at 4 weeks. This pressure change occurs in association with a decrease in heart rate from 204 ± 3 to 123 ± 6 beats per minute.¹⁹ In the studies of normal blood pressure in large animal neonates restraint artifacts have confounded the results. However clinical experience suggest that most large animal neonates make a rapid transition from the fetal low vascular resistance circulatory system to a physiologic state similar to adults. But a few retain the low vascular resistance (low blood pressure) circulatory system and maintain excellent perfusion. These patients may be retaining the fetal baroreceptor set point having delayed transition to the higher vascular resistance/blood pressure physiology of the adult. Critically ill neonates are more likely to retain the low vascular resistance and low baroreceptor set point. In these patients blood pressure cannot be used as the only surrogate for perfusion and absolute blood pressure numbers make poor and sometimes dangerous therapeutic goals.

The influence of the parasympathetic system on resting heart rate appears to increase with maturation.²⁰ Studies in puppies and kittens suggest that sympathetic innervation is also functionally incomplete at birth. Despite evidence of structural parasympathetic maturity, chronotropic responses in puppies at any given level of neural stimulus are less as compared with adult dogs, and before 14 days of age, there is minimal increase in heart rate in association with atropine administration, suggestive of a lack of vagal tone. In kittens, vagal stimulation was found to have no effect on heart rate until 11 days of age. These findings suggest a lack of full cardiac autonomic development during the neonatal period in kittens and puppies and help to explain why atropine may not be effective in neonatal resuscitation.^{21,22} Clinical observations strongly suggest that foals, calves, crias, lambs and kids have functionally intact sympathetic and parasympathetic cardiac control.

Resetting the arterial baroreflex is defined as a change in the relationship between arterial pressure and heart rate or between pressure and sympathetic and parasympathetic nerve activities.²⁰ The sensitivity of the baroreflex changes with maturation, and shifts (resets) toward higher pressures. This shift occurs during fetal life, is present immediately after birth, and continues with postnatal maturation, paralleling the naturally occurring increase in blood pressure. The mechanisms regulating developmental changes in baroreflex sensitivity and controlling the resetting of the baroreflex are poorly understood. Changes in the relationship between arterial pressure and sympathetic activity or heart rate occur at the level of the baroreceptor itself (peripheral resetting) and from altered coupling within the central nervous system of afferent impulses from baroreceptors to efferent sympathetic or parasympathetic activities (central resetting). These

findings suggest that factors other than the maturational increase in blood pressure influence the ontogenic changes in the arterial baroreflex. In all species the baroreceptor reflexes exhibit depressed sensitivity at birth, with a gradual postnatal maturation to adult levels.¹⁸ Differential rates of maturation of these systems influence the ability of the developing animal to maintain adequate blood pressure and organ blood flow.²⁰ At the time of birth the baroreceptor reflex has been thought to be absent in puppies but becomes apparent by 4 days of age.²² Before 4 days of age, anoxia (10 minutes) results in profound bradycardia (45 beats per minute) and marked hypotension (systolic blood pressure of 23 mm Hg).²³ Remarkably, circulatory failure does not occur at such low systolic pressure in the neonate, and puppies may be readily revived provided that the systolic blood pressure remains greater than 8 mmHg consistent with retention of the fetal low-resistance–high-flow circulatory system.²³ Studies evaluating heart rate response to hypoxia (decrease in inspired oxygen from 21% to 17% fraction of inspired oxygen) in a variety of newborn unanesthetized mammalian species failed to detect an alteration in heart rate.²⁴ Although as stated above most large animal neonates make a smooth transition to the adult physiology, clinically we recognize a population of critically ill neonates which seem to retain the fetal baroreceptor set point and thus have what appears to be an inappropriate bradycardia in response to hypoxemia with low blood pressures. They appear to be retaining the fetal response to hypoxemia. This autonomic dysregulation may be transient but while present requires careful medical management. In general, when this problem is present the neonate does not respond well in adrenergic support. In any case this inappropriate cardiovascular physiology in these hypoxemic neonates is not vagally mediated. It is far more appropriate to supplement oxygen than to give parasympatholytic agents, such as atropine, the administration of which only exacerbates cardiac hypoxemia via increasing oxygen demand in the face of hypoxemia.⁶

Functional closure of the ductus arteriosus is thought to occur in almost half of neonates by 24 hours and in 90% by 48 hours. Until anatomic closure which occurs within weeks, the neonate possesses a unique tool to deal with pulmonary hypertension.²⁵ Pulmonary hypertension may occur secondary to hypoxemia or, more commonly in my clinical experience, secondary to sepsis. In the adult pulmonary hypertension will result in the combination of decreased gas exchange and decreased left sided cardiac output resulting in tissue hypoxia and ischemia. In the neonate with anatomically patent ductus arteriosus and foramen ovale gas exchange may be compromised because of poor pulmonary perfusion resulting in hypoxia but because of the right to left shunt, left sided cardiac output will be maintained eliminating the ischemia and increasing the likelihood of survival.

Respiratory System

The developmental maturity of the lungs vary from species to species. Kittens, calves, and humans have relatively few alveoli at birth whereas lamb lungs are quite well developed.²⁶ The few studies that specifically address postnatal lung development in dogs present conflicting findings. Just as with the development of nephrons in the kidney, biological variation may contribute significantly to this difference. The degree of lung maturity at postnatal day 11 in dogs appears to be comparable to humans at birth. Evidence of lung development and growth activity was noted at the age of 8 weeks. In puppies it has been estimated that the maximal functional efficiencies of the dog lung are not reached until about 1 year in dogs compared to 20 years in humans.²⁶

Immaturity of chemoreceptor responses to hypoxia and poor sensitivity to CO₂ levels may result in mild hypoxemia and hypercapnia. Mild concurrent metabolic alkalosis often balances the hypercapnia resulting in a normal pH. Stimulation of the genital or umbilical region induces reflex respiration in the neonatal puppy and may be clinically used to stimulate respiration in the immediate neonatal period.^{6,27}

Gastrointestinal System

The GI is undergoing rapid development at the time of birth in all species. It increases 80% in length and 30% in diameter in the first 10 days of life. Maturation is incomplete until after weaning. Gastric acid secretion does not occur until after the initial period when macromolecules (IgG, cytokines, trophic hormones, etc.) are being transported intact through the GI mucosa. This period, which varies from species to species, is at least 24 hours but in the rat acid secretion does not occur during the first 18 days after birth (until weaning). Fetal intestinal epithelial cells have been transporting trophic macromolecules from ingested amniotic fluid during the last trimester of fetal life. Their life span is approximately 3 weeks and they can be found in lambs for at least 5 days, in calves for 2 weeks and in pigs up to 19-21 days. Although they retain their ability to uptake intact macromolecules from the GI lumen most transport slows dramatically by 6-12 days. Some neonatal epithelial cells also develop the ability to transport intact macromolecules. Although I have no supporting evidence I have often wondered if this intact macromolecule transport system which often works (depending on the species) though nonselective pinocytosis might be one reason translocation of bacteria occur more frequently during the neonatal period.

The regulation of the timing and nature of GI and liver growth is complex and involves multiple and often redundant factors. Among these factors are intrinsic cell programs or signals arising from gene expression, as well as extracellular signals, such as peptide growth factors, hormones, nutrients, and microbes, which originate from surrounding cells, the blood, and the gut lumen.²⁸ Another important aspect of growth in the gut is the continual proliferation, migration, and loss of epithelial cells along the mucosal surface. In the small intestine, this process involves four cell lineages (absorptive enterocytes, goblet cells, Paneth cells and endocrine cells) that differentiate from one pluripotent stem cell located in the crypt. An increase in circulating fetal glucocorticoid concentration just before and during vaginal birth is an important trigger of gut functional development.

The GI tract develops in response to numerous trophic signals. The term trophic actually means “of or pertaining to nutrition” and, in the case of the gut, nutrients present in amniotic fluid, colostrum and fresh milk are a major trophic influence. There are numerous extracellular trophic signals including foods, nutrients, peptide growth factors, gut peptide hormones, steroid and thyroid hormones, microbes, and neural inputs. The cells in the fetal and neonatal GI tract and liver are influenced by extracellular signals from multiple sources including (1) blood-borne factors in the circulation such as hormones that act via endocrine mechanisms; (2) luminal factors derived from amniotic fluid, mammary secretions, or microbes; and (3) local factors secreted via autocrine or paracrine mechanisms from surrounding cells.

Intestinal microbes exert trophic effects on the gut, as evidenced by increased epithelial cell proliferation, mucosal thickness, and lymphoid cell density.²⁸ The neonatal gut is sterile, but colonization occurs rapidly during the early neonatal period and plays a critical role in development of mucosal immune function. Microbes also produce bioactive molecules and substrates, including toxins and short-chain fatty acids that influence the proliferation and function of mucosal epithelial and immune cells. Nutrition is perhaps the most potent trophic stimulus of GI tract growth. The diet acts directly by supplying nutrients for growth and metabolism of mucosal cells, but it also acts indirectly by triggering the release of local growth factors, gut hormones, and activating neural pathways. Membrane receptors and transport proteins act as chemical sensors that signal the presence of nutrients via enteric nerves to mediate local GI function and also peripheral responses via the extrinsic nervous system. Maternal malnutrition and neonatal starvation cause reduced gut tissue mass, shortened villi, and generalized increased catabolism and decreased protein synthesis. However, the route of nutrient input, either enteral or parenteral, has a critical impact on the trophic response. In the late-gestation fetus, the onset of amniotic fluid swallowing coincides with increased intestinal growth and development. Studies in fetal sheep and pigs have shown that preventing this process by esophageal ligation suppresses intestinal growth. In the neonate, total parenteral nutrition (TPN) leads to significantly reduced growth and atrophy of the intestinal mucosa. The TPN-induced intestinal atrophy is associated with reduced cell proliferation, villus height, and protein synthesis and increased apoptosis and proteolysis. Studies with neonatal animals and human infants show that the lack of enteral nutrition is also associated with reduced secretion of many gut peptide hormones and growth factors. Animal studies have shown that several growth factors and gut peptides can prevent intestinal atrophy when coinjected with TPN. The practice of feeding small volumes of enteral nutrition, known as “trophic feeding,” has been shown to enhance GI motility and other functions. An additional consideration is whether to provide enteral nutrition as a bolus, or continuously. Studies in piglets suggest that, in comparison with continuous feeding, bolus feeding resulted in increased gut growth; however, this does not appear to be linked to secretion of trophic gut peptides.

Many of the trophic peptide growth factors are present in fresh milk, but not milk replacers, suggesting a beneficial advantage of feeding fresh milk because of a greater trophic effect on the GI tract.²⁸ However, the most significant advantage of fresh, species matched milk in the neonatal intestine may be related not to growth but rather to mucosal barrier and immune function. It was Paul Ehrlich in 1891 who first recognized the importance of colostrum transfer of protective factors. Colostrum is tailored for the neonate who has yet to develop a complete complement of immune functions. Certain agents in colostrum initiate or augment functions which are otherwise poorly expressed in the neonates. In fact, without some of the agents in colostrum, immune development will be delayed. Equine neutrophils only become mature killing cells after exposure to substances in colostrum. Certain immune functions that are initially absent in neonates are replaced by factors in colostrum. In addition, defense agents in colostrum have enhanced survival in the gastrointestinal tract of the recipient compared to their plasma derived counterparts. Also, defense factors in colostrum protect without provoking damaging inflammation and some agents inhibit inflammation both allowing targeting of pathogens without allowing the inflammatory reaction to disrupt the development of the neonate's gastrointestinal tract. There are also agents in colostrum that alter the physiologic and biochemical state of the gastrointestinal tract from one suited to fetal life to one appropriate to extrauterine life. Finally and perhaps most importantly, growth factors in colostrum augment the proliferation of the commensal enteric bacteria. Since the gastrointestinal tract is the most likely portal of entry of pathogens, the action of colostrum in preventing luminal establishment, proliferation and invasion of pathogens is vital in protecting the neonate from sepsis.

Antimicrobial factors in colostrum include proteins such as lactoferrin (bacteriostasis by Fe chelation), lactoferricin (causing bacterial killing), lysozymes (bacteriolysis by degrading peptidoglycans), MUCI (inhibits the binding of S-fimbriated *E coli* to epithelial cells), lactadherin (binds viruses so prevents epithelial attachment), oligosaccharides and glycoconjugates (receptor analogues which inhibit binding of enteric pathogens and toxins to epithelial cells) and monoglycerides and fatty acids (disrupts enveloped viruses, inactivate certain bacteria, defend against Giardia). Other important factors in colostrum include PAF acetylhydrolase (PAF-degrading enzyme; PAF is an important proinflammatory mediator in the GI with high levels in the neonate; this enzyme protects mucosal cells from damage caused by PAF by degrading it), erythropoietin which protects against apoptosis of intestinal epithelium, epidermal growth factor which has been shown to play an important role in mucosal barrier function in developing intestine, and down-regulates apoptosis of intestinal epithelium.

In the cat, as much as 25% of a kitten's serum antibodies may be derived via transplacental antibody transfer. In comparison, 5% to 10% of canine neonatal serum antibodies are derived from transplacental transfer. At birth, canine and feline neonates are antibody deficient and immunologically incompetent, with the acquisition of passive immunity requiring adequate ingestion and absorption of colostrum during the first 24 hours of life. There is no transplacental transfer of antibodies in foals, calves, lambs, kids or crias. So in all species, colostrum transfer of immunoglobulins and other immunomodulators and protective factors is very important. Absorption of antibodies (transfer to blood) decreases markedly in all domestic species after 12 hours but transfer of local immune factors as mentioned above may continue to have positive effects. So even when a neonate cannot be fed because of concurrent disease early in the neonatal period, beginning nutrition with colostrum can be very beneficial.^{29,30}

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