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Endocrine physiology in the newborn

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ABSTRACT

Evaluation of suspected endocrine pathology in newborn infants requires knowledge of the dynamic changes that characterize normal hormonal function in the neonatal period. This article reviews normal endocrine physiology as it pertains to common clinical scenarios encountered in neonatal surgical patients. Topics covered include thyroid and adrenal function as well as glucose and calcium metabolism.

The perinatal period is characterized by dynamic changes in multiple hormone systems. This review discusses normal neonatal endocrine physiology as it relates to thyroid function, adrenal function, glucose homeostasis, and calcium metabolism, with occasional reference to pathologic states. Purposefully omitted is a discussion of disorders of sexual differentiation. With a firm understanding of the normal fluxes in neonatal endocrine physiology, we hope that the pediatric surgeon can make informed decisions regarding the evaluation and treatment of possible pathology.

Thyroid

Thyroid hormone has important effects on diverse physiologic processes including cellular proliferation and differentiation, energy balance, and cardiovascular physiology. In particular, thyroid hormone is essential for normal growth and development, and hypothyroidism is the leading cause of mental retardation worldwide. Abnormal thyroid function tests are common in hospitalized infants, and a clear understanding of normal thyroid physiology will assist with appropriate evaluation and treatment, as well as avoiding unnecessary testing and interventions.

The thyroid gland originates as an outpouching from the base of the tongue around gestational week 4 and descends caudally to its final position by week 7.[1] The thyroglossal tract along which the thyroid descends is normally obliterated, but remnants of this tract may manifest later as thyroglossal duct cysts. The fetal thyroid can concentrate iodide and produce thyroid hormone by gestational week 12, but thyroid hormone synthesis increases substantially in the third trimester when maturation of the hypothalamus and pituitary leads to increased secretion of thyroid-stimulating hormone (TSH), the primary stimulus for thyroid hormone production. Thyroid hormone regulates its own secretion by exerting negative feedback on both the pituitary and the hypothalamus; for this reason, in the setting of normal feedback regulation, persistently elevated levels of TSH are the most sensitive indicator of primary thyroid dysfunction.

The thyroid hormones, thyroxine (T4) and triiodothyronine (T3), are hydrophobic iodinated molecules that circulate bound to serum binding proteins (primarily thyroid-binding globulin). The unbound or "free" fraction of each thyroid hormone is biologically available and enters target cells through specific transporters and possibly by passive diffusion. The action of thyroid hormone is mediated by binding to thyroid hormone receptors (TRs) in the cell nucleus, resulting in changes in gene transcription. Although T4 is the predominant circulating thyroid hormone, T3 is considered the biologically active thyroid hormone because of its 15-fold greater binding affinity for TRs. A family of enzymes called iodothyronine deiodinases is responsible for activating circulating T4 to T3 or for inactivating both T4 and T3 to inert metabolites. Alterations in this peripheral metabolism contribute to the normal changes in thyroid hormones observed after birth, as well as to abnormal thyroid function in states such as nonthyroidal illness (NTI).[2]

Dietary iodine is an essential requirement for the synthesis of thyroid hormones, and iodine deficiency is the most important cause of hypothyroidism worldwide. Infants are at high risk of iodine deficiency due to their proportionally greater daily iodine requirement than adults. Since the bulk of fetal iodine stores are laid down in the third trimester, premature infants have decreased

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iodine stores and are at even higher risk of iodine deficiency than term infants. This risk may be exacerbated by the low iodine content of enteral and parenteral nutritional regimens commonly used in intensive care nurseries.[3] Iodine excess can also cause hypothyroidism in neonates by inhibiting the release of thyroid hormone from the gland (the Wolff–Chaikoff effect). Hypothyroidism has been described in newborns following exposure to iodine-containing antiseptics or contrast agents.[4,5]

Circulating levels of T4 and T3 are relatively low prior to birth, and the fetus is dependent on maternal thyroid hormone through the third trimester, which is a critical window for brain development.[6] A dramatic increase in TSH secretion occurs within hours after birth, with levels reaching 60–80 mIU/L within 24 h and then decreasing over the next several days.[7] This TSH surge leads to increased levels of circulating T4 and T3, and this rise is supported by increased peripheral activation of T4 to T3 and decreased inactivation of both thyroid hormones. Awareness of the normal neonatal surge in TSH is critical to avoid misinterpreting a modestly elevated TSH in the first 1–2 days of life as diagnostic of hypothyroidism.

Premature and low-birth-weight neonates have a high incidence of abnormal thyroid function, which is present in 50% or more of infants born below 28 weeks of gestational age.[8] Compared to term infants, preterm infants have lower T4 levels at birth that frequently decrease (rather than increase) in the first weeks of life,[9] likely due to a combination of factors including deprivation of maternal thyroid hormone, immaturity of the thyroid axis and of peripheral deiodination, nonthyroidal illness, and exposure to dopamine or glucocorticoids (which suppress TSH secretion). The pattern of low levels of T4 with normal TSH (termed "hypothyroxinemia of prematurity") is correlated with poor outcomes in preterm infants[10]; however, treatment has shown no clear evidence of benefit,[11,12] and one study suggested a possible increased risk of necrotizing enterocolitis in infants treated with levothyroxine.[13]

Thyroid function abnormalities induced by NTI are commonly encountered in hospitalized patients, particularly those who are critically ill. The typical laboratory pattern is low circulating levels of T3 with inappropriately normal or low TSH; levels of T4 may also be low if the illness is severe or prolonged. The mechanisms underlying these changes are incompletely understood but involve changes in hypothalamic–pituitary response; decreased production of T4; decreased activation of T4 to T3; and increased inactivation of both T4 and T3. Given the correlation between thyroid function abnormalities in NTI and severity of illness, many have speculated that treatment of NTI with thyroid hormone may improve clinical outcomes. However, such treatment was found to have no benefit in large randomized, controlled trials in adults.[14–16] Although data in neonates are limited, at present there is no clear evidence of benefit from treating low T4 or T3 levels in neonates, including high-risk groups such as preterm infants or those recovering from cardiac surgery.[17,18]

Clinical evaluation of thyroid dysfunction may be challenging in neonates, since signs are often nonspecific and may be absent even with a moderate degree of thyroid dysfunction. Signs of hypothyroidism include hypothermia, lethargy, poor feeding, poor weight gain, dry skin, constipation, umbilical hernia, periorbital edema, and macroglossia. Hyperthyroidism in the neonatal period is very rare and is usually due to maternal Graves disease; signs may include hyperthermia, jitteriness, irritability, increased appetite or poor feeding, poor weight gain, frequent stools, and goiter.

Thyroid hormone is critical for normal neurodevelopment, and untreated hypothyroidism in early life can result in severe developmental abnormalities including mental retardation and delays in motor development. Therefore, early identification and treatment of neonatal hypothyroidism is critical to optimizing outcome.[19] However, in hospitalized infants, thyroid function abnormalities due to NTI or prematurity are common, and treatment of these conditions—unlike true congenital hypothyroidism—has no demonstrated benefit. Since the goal of evaluation should be to identify clinically significant hypothyroidism that will benefit from treatment, thyroid function testing in hospitalized infants—other than that indicated by newborn screening protocols—should be performed based on specific clinical suspicion of thyroid disease. Laboratory assessment for hypothyroidism in an infant should include measurement of serum TSH and free T4 concentrations; serum T3 concentration is rarely useful and should not be measured routinely. Although "direct" assays for free T4 are widely available, they may be less reliable in the setting of altered thyroid hormone binding, which is frequently present in critical illness; therefore, free T4 measurements should be interpreted with caution in such patients or replaced by measurement of total T4 concentration and the thyroid hormone binding ratio. Neonatal thyroid function tests should be interpreted based on age-specific normal ranges, including gestational age-specific norms for preterm infants, which can be found in Ref. 20.

The most common cause of congenital hypothyroidism (85% of cases) is thyroid dysgenesis or failure of normal formation of the gland. Thyroid dysgenesis is almost always sporadic, although rare familial cases are due to genetic defects in factors necessary for thyroid development (e.g., *PAX8* and *NKX2.1*). Most other cases of congenital hypothyroidism are caused by enzymatic defects in thyroid hormone synthesis (10% of cases). Rarely, congenital hypothyroidism may be central in origin due to hypothalamic or pituitary lesions; in such cases, serum levels of free T4 are low with inappropriately normal or low levels of TSH, and additional pituitary hormone deficits are usually present.[21]

If primary hypothyroidism is confirmed based on elevated serum TSH and low serum-free T4, treatment should be instituted with levothyroxine 10–15 mcg/kg daily with the goal of rapidly increasing free T4 to the upper half of the normal range and normalizing TSH.[19] In an ill neonate, repeat testing every 1–2 weeks is indicated until thyroid function has normalized. Congenital hypothyroidism is usually permanent but may be transient in 10–30% of cases[22,23]; however, once treatment is initiated in the newborn period, it is often continued through the critical first 3 years of brain development, at which time a trial off therapy may be considered.

Adrenal

Cortisol produced by the adrenal gland is a critical mediator of the physiologic response to stress. Effects of cortisol include maintenance of vascular tone, provision of metabolic substrate to vital organs, and inhibition of the immune response. Although absolute adrenal insufficiency is rare, relative adrenal insufficiency may exist when adrenal cortisol production is insufficient to cope with severe physiologic stress, which may result in decompensation and death. Although the precise definition of adrenal insufficiency in neonates is debated, its prevalence may be as high as 50% in critically ill term and preterm neonates,[24] and it is associated with adverse outcomes including mortality.[25,26] In a study of full-term neonates with sepsis, adrenal insufficiency was associated with a mortality rate of 86%, compared with 12.5% in infants with normal adrenal function.[25]

The adrenal glands develop around gestational weeks 6–8, and pituitary corticotrophs are evident and functional before the end of the first trimester. Adrenal growth and cortisol production is driven by adrenocorticotrophic hormone (ACTH), which is secreted by pituitary corticotrophs in response to hypothalamic corticotrophin-releasing hormone (CRH). Cortisol regulates its own production by

suppressing ACTH through negative feedback on both the hypothalamus and pituitary. Because ACTH is required for adrenal growth, persistently low levels of ACTH may lead to adrenal atrophy and secondary adrenal insufficiency. Secondary adrenal insufficiency in neonates is most commonly due to prenatal or postnatal treatment with glucocorticoids but can also occur in the setting of congenital hypopituitarism.

Since adrenal production of aldosterone is regulated independently by the renin–angiotensin system, aldosterone deficiency occurs only in cases of primary adrenal insufficiency, in which the adrenal gland itself is dysfunctional. The most common cause of primary adrenal insufficiency is congenital adrenal hyperplasia (CAH) due to deficiency of the enzyme 21-hydroxylase, which is necessary for adrenal synthesis of both cortisol and aldosterone. In addition to adrenal insufficiency and potentially life-threatening salt wasting, affected patients develop marked elevation of the steroid precursor 17-hydroxyprogesterone and of adrenal androgens, which manifests as virilization of affected female infants. Other causes of primary adrenal insufficiency in neonates include failure of normal adrenal gland development (e.g., mutations in *SF1* or *DAX1*), rarer forms of congenital adrenal hyperplasia, and bilateral adrenal injury or hemorrhage.

Clinical manifestations of adrenal insufficiency in the neonate are usually nonspecific but are important to recognize because of the associated morbidity. Adrenal insufficiency may cause poor growth, hypoglycemia, and hypotension resistant to volume and vasopressor therapy. Hyponatremia and hyperkalemia due to aldosterone deficiency may be present in primary adrenal insufficiency. The presence of genital ambiguity or virilization of a female infant should prompt immediate evaluation for classical CAH, which can lead to severe salt wasting and death within the first 2 weeks of life if untreated.

Because absolute adrenal insufficiency is rare, in practice, the challenge is to identify which severely ill neonates have relative adrenal insufficiency that is likely to benefit from treatment. Studies have used various protocols to evaluate suspected adrenal insufficiency in neonates, but the optimal approach to diagnosis is still uncertain. The primary indication for evaluation of adrenal function in an ill neonate is development of volume- and vasopressor-resistant hypotension. In the setting of sepsis, critical illness, or other severe stress, a random cortisol level < 15 mcg/dL should raise suspicion for adrenal insufficiency and prompt further evaluation (Figure).[25] Diagnosis of adrenal insufficiency requires an ACTH stimulation test demonstrating inadequate cortisol secretion in response to ACTH. Based on available data in neonates, we recommend drawing baseline levels of ACTH and cortisol, followed by another cortisol level 30–60 min after an intravenous bolus dose of ACTH 1 mcg/kg.[24] A stimulated cortisol concentration less than 17 mcg/dL is consistent with adrenal insufficiency. If primary adrenal insufficiency is suspected, additional evaluation may include serum and urine electrolytes and plasma renin activity to assess for aldosterone deficiency. Serum levels of 17-hydroxyprogesterone should be measured if classical CAH is suspected.

Treatment with glucocorticoids improves cardiovascular status in term and preterm infants with vasopressor-resistant hypotension and documented adrenal insufficiency.[27,28] Such infants should be treated with intravenous hydrocortisone 50 mg/m^2 body surface area per day, divided every 6 h. While empiric glucocorticoid treatment of refractory neonatal hypotension has been used, it is not recommended in the absence of documented adrenal insufficiency due to lack of clear benefit and a possible increased risk of complications such as gastrointestinal perforation.[29] Evaluation of adrenal function should be considered prior to surgery in at-risk patients, such as those treated with prolonged courses of glucocorticoids, if their maintenance steroid dose is less than the recommended "stress dose" of hydrocortisone 50 mg/m^2/day (or equivalent). Patients in whom adrenal function is uncertain and preoperative testing is not possible may receive empiric treatment with hydrocortisone 50 mg/m^2 body surface area daily, divided every 6 h. At this dose, hydrocortisone (but not prednisolone or dexamethasone) has sufficient mineralocorticoid action to obviate the need for additional mineralocorticoid supplementation.

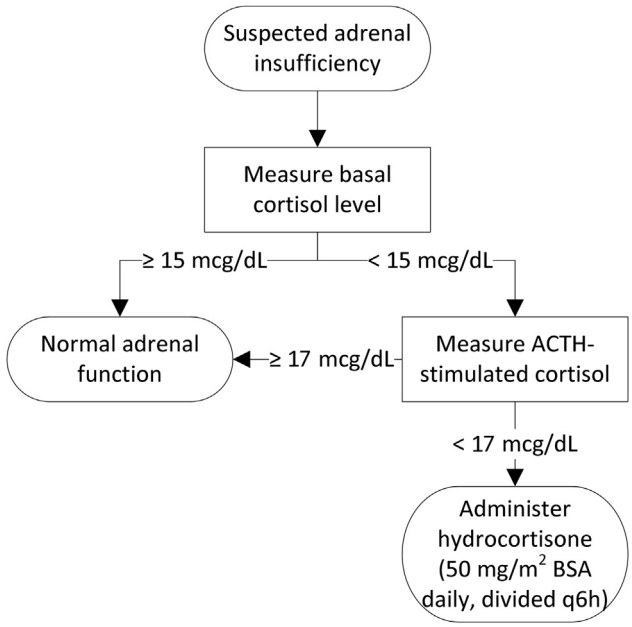

Fig. Evaluation of suspected neonatal adrenal insufficiency. BSA, body surface area = [Length (cm) . × Mass (kg)/3600]$^{1/2}$.

Glucose metabolism

Glucose is the primary metabolic substrate used by most tissues to generate energy for cellular processes. Plasma glucose levels are therefore tightly regulated to ensure adequate energy supply for vital functions. The brain is particularly vulnerable to hypoglycemia because of its requirement for a continuous supply of glucose to support its high rate of metabolic activity. Insulin is the primary hormone responsible for lowering plasma glucose by decreasing hepatic breakdown of glycogen (glycogenolysis) and synthesis of new glucose (gluconeogenesis), and by increasing peripheral glucose uptake. In contrast, multiple counterregulatory hormones—including glucagon, epinephrine, cortisol, and growth hormone—defend against hypoglycemia by increasing glycogenolysis, gluconeogenesis, and the oxidation of fatty acids to generate energy for gluconeogenesis. Fatty acid oxidation also generates ketones, which serve as the primary alternative metabolic substrate for the brain when plasma glucose is low.

Maintenance of euglycemia requires balancing glucose utilization with intake and endogenous production. The newborn period is a time of high risk for hypoglycemia due to factors on both sides of this equation. Neonates have higher basal glucose requirements than older children and adults, likely due to the larger size of the newborn brain relative to body size. Increased metabolic needs in neonates may be driven by physiologic stress such as asphyxia, respiratory distress, or sepsis. Hyperinsulinism may also increase glucose utilization. Normal newborns are adapted to receive minimal exogenous nutrition for several days until the maternal milk supply develops, and thus, must produce sufficient endogenous glucose to supply their needs. To do so, the neonate must

have adequate substrate (including stores of glycogen, fat, and protein); intact enzymatic pathways for glycogenolysis, gluconeogenesis, amino acid metabolism, and fatty acid oxidation; and normal hormonal regulation of these processes. Glycogen and fat stores are primarily laid down in the third trimester, leaving preterm infants more vulnerable to hypoglycemia. Hypoglycemia may also be caused by inborn errors of metabolism in these enzymatic pathways, by hyperinsulinism, or by deficiency of cortisol (adrenal insufficiency) or growth hormone (as in hypopituitarism).

Marked changes in glycemia occur within the first hours after birth. At birth, the newborn's plasma glucose concentration reflects that of its mother. After the umbilical cord is clamped, glucose levels fall rapidly during the first few hours postnatally, sometimes decreasing transiently to as low as 20–30 mg/dL. Thereafter, a normal counterregulatory response including secretion of epinephrine and cortisol increases plasma glucose. While severe symptomatic hypoglycemia can cause brain injury, it is not clear whether transient asymptomatic hypoglycemia in normal infants in the first days of life, even if severe, has any detrimental effect on long-term outcome. Therefore, the true "normal" range of plasma glucose during the first few hours and days after birth is not well defined in asymptomatic infants. Consensus guidelines are available for evaluation and management of neonatal hypoglycemia, although these are relevant to healthy term infants, and the evidence to support most specific recommendations is sparse.[30] The guidelines suggest the lower limit of plasma glucose (measured prior to feeding) as 40 mg/dL in the first 3 h of life and 45 mg/dL thereafter; we suggest a lower limit of 60 mg/dL beginning at 72 h of life. Intravenous glucose should be given to symptomatic infants with hypoglycemia and to asymptomatic infants with plasma glucose below 25 mg/dL (in the first 3 h) or 35 mg/dL (between 4 and 24 h), with the goal of maintaining prefeed plasma glucose levels above 45 mg/dL. Asymptomatic infants with milder hypoglycemia may be managed initially with enteral feeding.[30]

Any newborn found to have persistent hypoglycemia should be evaluated to determine its etiology. The most common cause of persistent neonatal hypoglycemia is hyperinsulinism, and this diagnosis should be considered if after 24 h of life the exogenous glucose infusion rate required to maintain euglycemia exceeds 8 mg/kg/min, suggesting that excess glucose utilization is present. It is critical to differentiate hyperinsulinism from other causes of hypoglycemia because insulin is a potent inhibitor of ketone formation. Because hyperinsulinism deprives the brain of both glucose and its alternative metabolic substrate, recurrent hypoglycemia due to hyperinsulinism can cause permanent neurological impairment including moderate to severe mental retardation in 32% of patients and epilepsy in 24%.[31]

Transient hyperinsulinism lasting days to weeks may be seen in infants of mothers with diabetes, infants who are large for gestational age, or newborns who suffer severe perinatal stress or asphyxia. Permanent congenital hyperinsulinism is due to a genetic defect in one of several genes regulating insulin secretion. Because of the risk of permanent neurologic damage, hyperinsulinemic hypoglycemia must be managed aggressively. Diazoxide may be used to treat many forms of both transient and permanent hyperinsulinism, but some cases of the latter are amenable to surgical treatment with either resection of a focal source of hyperinsulinism or near-total pancreatectomy for diffuse disease.[32,33] If hyperinsulinism is suspected, an endocrinologist should be consulted, particularly if hypoglycemia is severe, prolonged, or unresponsive to diazoxide.

Clinical signs of neonatal hypoglycemia include those related to the adrenergic response (tachypnea, jitteriness, and irritability) and those due to inadequate glucose supply to the brain (hypothermia, apnea, bradycardia, poor feeding, decreased tone, lethargy, and seizure). Any newborn exhibiting such signs should be evaluated for hypoglycemia. For convenience, whole blood glucose levels are commonly checked in newborns by heel stick or finger stick; such values, however, can be inaccurate due to preanalytic factors (e.g., squeezing the foot/digit to obtain the sample) and to the imprecision of many point-of-care glucose tests in this setting.[34–36] Therefore, a low blood glucose concentration detected by point-of-care testing or a clinical suspicion for hypoglycemia should be confirmed by measuring plasma glucose in a laboratory. A "critical sample" obtained at the time of hypoglycemia should include serum concentrations of glucose, insulin, free fatty acids, ketones (such as beta-hydroxybutyric acid), electrolytes, and lactate. If serum ketones are not available, urine ketones may be substituted. In the setting of hypoglycemia, inappropriately low levels of ketones indicate hyperinsulinism or a defect of fatty acid oxidation; a detectable serum insulin level, low levels of free fatty acids, and an elevated glucose infusion rate are highly suggestive of hyperinsulinism. Appropriately elevated levels of ketones and free fatty acids suggest another cause of hypoglycemia such as increased consumption (e.g., due to intercurrent illness), inadequate glycogen stores, an inborn error of metabolism, or a deficiency of hormonal counterregulation. Serum levels of cortisol and growth hormone may be measured during hypoglycemia and can rule out a deficiency if robust, but low levels are nonspecific and are not diagnostic of a hormone deficiency.[37]

Calcium

Problems of mineral homeostasis commonly encountered in hospitalized newborns include acute hypocalcemia and abnormal bone metabolism. Calcium plays a central role in skeletal and cardiac muscle function and cell signaling, while both calcium and phosphate are critical to normal bone development and mineralization. During fetal life, calcium is derived from the maternal circulation, and 80% of fetal calcium stores are accrued in the skeleton during the third trimester of pregnancy.[38] Because preterm infants have both increased requirements for and decreased stores of calcium and phosphate compared to term infants, specialized preterm infant formulas or human milk fortifier that provide adequate amounts of these minerals are generally recommended for infants under 2000 g.[39] Parenteral nutrition may provide inadequate amounts of calcium and phosphate for very preterm infants, and prolonged need for parenteral nutrition may impair bone health.[40] Increasing the calcium content and minimizing the aluminum content of parenteral nutrition may improve bone health,[41,42] but high-quality data on long-term outcomes are lacking.[43]

Several additional risk factors contribute to abnormal bone metabolism in hospitalized neonates. Some commonly used medications have adverse effects on bone formation. Glucocorticoids decrease bone density through multiple pathways that both increase bone resorption and decrease bone formation.[44] Loop diuretics such as furosemide may be associated with decreased bone density, possibly by promoting calciuresis. Mechanical force exerted by muscle contraction is a critical stimulus for bone growth, and immobilization—whether due to underlying illness or medication-induced paralysis—increases bone resorption[45] and is a common cause of decreased bone strength in critically ill patients. Combinations of these factors are present in many hospitalized neonates and may contribute to increased bone fragility and fracture risk, so care must be taken to minimize these risk factors and to optimize nutrition and bone health in this population.

The hormonal systems regulating calcium homeostasis are designed primarily to defend against hypocalcemia. About half of plasma calcium circulates in the physiologically relevant unbound or "ionized" form, with most of the remainder bound to serum albumin. The parathyroid glands monitor plasma calcium levels via a specific calcium-sensing receptor (CaSR) and secrete parathyroid hormone (PTH) in response to hypocalcemia. PTH raises plasma calcium by stimulating bone resorption to mobilize skeletal calcium stores, as well as by increasing the conversion of 25-hydroxyvitamin D (25-OHD) to its active form, 1,25-dihydroxyvitamin D (1,25-OH_2D), which in turn increases absorption of dietary calcium and phosphate from the intestine. As plasma calcium rises, activation of the CaSR suppresses PTH release, completing the negative feedback loop. A variety of conditions that affect parathyroid function can lead to neonatal hypocalcemia. Transient hypoparathyroidism may occur in infants with hypomagnesemia and infants of mothers with diabetes mellitus or hyperparathyroidism, while permanent hypoparathyroidism due to failure of normal gland formation occurs in DiGeorge syndrome (22q11 deletion) and several rarer genetic syndromes.

Vitamin D is believed to be required for absorption of calcium from the gastrointestinal tract, and although this process may be at least partly vitamin D independent, vitamin D deficiency in the neonatal period may contribute to hypocalcemia and rickets. Vitamin D levels in newborn infants are related directly to maternal levels, and the high rate of maternal vitamin D deficiency has made this a common problem in infants as well.[46] Newborn infants should routinely receive at least 400 IU daily of vitamin D, except in the smallest infants (<1500 g) in whom 200 IU daily may be appropriate.[39,47] Because vitamin D is fat soluble, its absorption may be compromised in infants with cholestasis, fat malabsorption, or intestinal failure. Hepatic or renal disease may also contribute to hypocalcemia by interfering with the sequential activation of vitamin D in the liver (to 25-OHD) and kidney (to 1,25-OH_2D) that is necessary for its biological activity. In addition to hypoparathyroidism and vitamin D deficiency, other causes of hypocalcemia in the newborn period include birth asphyxia, blood transfusions, renal dysfunction, and excess phosphate intake.

Mild hypocalcemia is usually asymptomatic. Severe hypocalcemia usually manifests as neuromuscular irritability with muscle contractions, exaggerated reflexes, tetany, or seizure. The evaluation of neonatal hypocalcemia should focus on establishing whether the cause is related to hypoparathyroidism, inadequate vitamin D action, or another cause, since the treatment will vary based on the etiology. Plasma levels of total calcium may be low in the setting of hypoalbuminemia; in such cases, ionized calcium may be measured or the total plasma calcium concentration may be corrected for measured levels of serum albumin. In addition to measuring levels of calcium, phosphate, PTH, and 25-OHD, the laboratory evaluation of hypocalcemia should include serum electrolytes, magnesium, alkaline phosphatase, and an assessment of renal function. Hypocalcemia with elevated phosphate levels is suggestive of hypoparathyroidism, since PTH normally increases renal phosphate excretion; an inappropriately normal or low PTH in the setting of hypocalcemia will confirm the diagnosis. Low levels of 25-OHD (<20 ng/mL) are consistent with vitamin D deficiency; levels of 1,25-OH_2D do not correlate with overall vitamin D status and should not be measured except under rare circumstances. Elevated levels of alkaline phosphatase (>800 IU/L) that are not due to cholestasis should raise suspicion for rickets and prompt radiographic evaluation.[39]

Administration of calcium is the initial treatment for any cause of hypocalcemia. If hypocalcemia is severe or symptomatic, intravenous calcium may be required, but enteral calcium supplementation is appropriate for mild or moderately asymptomatic hypocalcemia. Vitamin D deficiency should be treated by supplementation to reach a goal 25-OHD concentration of >20 ng/mL. If hypoparathyroidism is diagnosed, treatment should include calcitriol (1,25-OH_2D) in addition to calcium supplementation. If hypoparathyroidism persists or if it occurs in the absence of a typical transient cause, a cause of permanent hypoparathyroidism should be sought, particularly DiGeorge syndrome, in which a subtle cardiac malformation or immunodeficiency otherwise may be overlooked.

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