A blood test performed at 12 hours of age in a newborn shows a total serum calcium concentration of 6.5 mg/dL (1.63 mmol/L). The ionized serum calcium concentration is 3.6 mg/dL (0.9 mmol/L).

Of the following, the MOST likely cause of these laboratory results is:

1. high phosphate feeding
2. intrauterine growth retardation
3. maternal diabetes
4. prematurity
5. vitamin D deficiency

You selected 1, the correct answer is 1.

In the term newborn, the normal concentration of total serum calcium at 12 hours of age ranges from approximately 7.0 to 10.0 mg/dL (1.8 to 2.5 mmol/L). The lower limit of ionized serum calcium concentration is approximately 4.0 mg/dL (1.0 mmol/L). Accordingly, the infant described in the vignette has biochemical evidence of hypocalcemia. Early neonatal hypocalcemia is defined as occurring within the first 3 days after birth. The most likely cause of early neonatal hypocalcemia is prematurity. The overall incidence of early neonatal hypocalcemia is approximately 30% among preterm infants, and the incidence varies inversely with gestational age. Hypocalcemia of prematurity is related in part to decreased exogenous calcium intake, transient functional hypoparathyroidism, and increased serum calcitonin.

Intrauterine growth retardation, in the absence of prematurity or perinatal asphyxia, is not an independent risk factor for the development of early neonatal hypocalcemia. In perinatal asphyxia, hypocalcemia is attributed to decreased calcium intake from delayed feedings, increased endogenous phosphate load, augmented calcitonin response, and end-organ parathyroid hormone resistance. Additionally, correction of metabolic acidosis with a base as a part of resuscitation may aggravate hypocalcemia by lowering the ionized calcium fraction.

Maternal diabetes can cause early neonatal hypocalcemia, particularly in the presence of prematurity and perinatal asphyxia. Hypocalcemia in an infant of a diabetic mother is correlated with the severity of maternal diabetes. At present, with the current strict management of maternal diabetes, the overall incidence of hypocalcemia among infants of diabetic mothers is no more than 17%. The cause of early neonatal hypocalcemia in maternal diabetes is related to magnesium metabolism. Excessive urinary loss of magnesium associated with maternal diabetes results in fetal magnesium deficiency and secondary functional hypoparathyroidism in the fetus and newborn.

High phosphate feeding is a prominent feature of late neonatal hypocalcemia, which is defined as hypocalcemia that occurs after the first 3 days of age. Hypocalcemia induced by high phosphate feeding usually occurs at about 7 days of age. The normally low neonatal glomerular filtration rate may contribute to hypocalcemia by limiting the ability to excrete the phosphate load. Late neonatal hypocalcemia was observed frequently among infants fed undiluted cow milk or evaporated milk that had a high phosphate content. With the introduction of adapted infant formulas,
however, late neonatal hypocalcemia has become rare.

Currently, there is no convincing evidence that vitamin D deficiency or abnormalities of vitamin D metabolism contribute to the pathogenesis of early neonatal hypocalcemia. In the absence of maternal malnutrition, the vitamin D stores in the newborn are generally adequate, as is the synthesis of various vitamin D metabolites.

References:

Content Specification(s):
Understand the etiology, clinical manifestations, laboratory features, and approach to therapy of neonatal hypocalcemia and hypercalcemia
During the discharge examination from the newborn nursery, a term female infant is noted to have bilateral swollen labia majora with slight hyperpigmentation and rugae. No masses are palpated in the labioscrotal folds. The clitoris appears normal-sized, and the vaginal opening and urethra are easily visualized.

Of the following, the MOST likely cause for these physical findings is maternal exposure to:

- androgens
- estrogens
- marijuana
- medroxyprogesterone
- thyroid hormone

You selected 1, the correct answer is 1.

Genital development can be influenced by a number of factors, such as the production of endogenous hormones, exposure to an exogenous source of hormones, a chromosomal abnormality, and the presence of an inherited enzymatic defect. The effect of hormones on the appearance of genitalia depends on the timing and duration of prenatal exposure. For example, androgenic drugs can cause masculinization or virilization of external female genitalia. In contrast, chromosomal abnormalities can affect the differentiation of internal sexual organs and lead to the development of ambiguous genitalia.

Prior to 6 weeks of age, both the wolffian and mullerian duct systems are present in the normal embryo, making male and female gonads indistinguishable. The tendency of the fetus, however, is to develop as a female, unless a Y chromosome is present. If present, a testes-determining factor induces differentiation of the gonads into testes, and female genital development is blocked. Leydig cells begin to produce testosterone, which acts on the wolffian duct to form the male internal genitalia: vas deferens, epididymis, and seminal vesicles. The testicles also produce an anti-mullerian hormone (AMH), also known as mullerian-inhibiting substance, which causes regression of the mullerian ducts. Formation of the phallus and scrotum (the external male genitalia) requires the conversion of testosterone to dihydrotestosterone (DHT) via 5-alpha-reductase and the presence of a specific androgen receptor. The testes migrate into the scrotum later in gestation.

If the Y chromosome is absent and there are two intact and normal functioning X chromosomes, the undifferentiated gonads of an embryo will develop into female organs.

The wolffian duct degenerates in the absence of androgens, and because no AMH is produced, internal female structures such as the fallopian tubes, uterus, and upper vagina develop from the müllerian duct. Similarly, in the absence of DHT, external genitalia do not fuse, thus allowing the folds and swellings to become labia and the genital tubercle to become the clitoris.

The external genitalia of the female infant described in the vignette are consistent with prenatal exposure to androgens or another virilizing drug. Although the labia...
most term female infants are swollen, the accompanying hyperpigmentation and rugae, as described for the infant in the vignette, are signs of masculinization. However, the normal-size clitoris and the easily visible urethra and vaginal introitus exclude the diagnosis of ambiguous genitalia. Estrogen exposure may cause breast enlargement in the term infant and withdrawal vaginal bleeding in the female infant, but it will not affect the appearance of the external genitalia. The long-acting progestin medroxyprogesterone also will not alter the appearance of the genitalia. Although an illicit substance such as marijuana and medications such as thyroid hormone may affect the fetus in general, neither will affect genital development, resulting in the physical findings described in the vignette.

References:

Content Specification(s):
Understand normal fetal sexual differentiation.
Please remember that you must answer all 10 of the questions in order to claim CME credit for this month.

A term infant who has macrosomia experiences repeated episodes of hypoglycemia during the first week of life. During these episodes, the infant presents with tremors, irritability, cyanosis, and refusal to feed. Her blood glucose concentration is 10 mg/dL (0.56 mmol/L), and plasma insulin concentration is markedly elevated at 20 mcU/mL (143.5 pmol/L). The infant has received a parenteral glucose infusion.

Of the following, the MOST appropriate initial drug of choice in the pharmacologic treatment of this infant is

- calcium channel blocker
- diazoxide
- epinephrine
- glucagon
- octreotide

You selected 4, the correct answer is 2.

The infant described in the vignette has symptomatic, refractory hypoglycemia resulting from hyperinsulinism. Diazoxide is the initial drug of choice in neonates who remain hypoglycemic despite repeated parenteral glucose infusions. Diazoxide inhibits the sulfonylurea receptor, a plasma membrane protein, with resultant blockage of insulin secretion from the pancreatic beta cells. Additionally, diazoxide stimulates catecholamine release, which increases hepatic production and decreases peripheral utilization of glucose. The usual effective dose of diazoxide for the management of hyperinsulinemic hypoglycemia in the newborn is 5 to 20 mg/kg per day administered orally at 8- to 12-hour intervals.

Because an influx of extracellular calcium is required for insulin secretion from the pancreatic beta cells, calcium channel blockers could play a potential role in the treatment of hyperinsulinemic hypoglycemia. However, the experience with these agents in the treatment of neonates who have refractory hypoglycemia is limited, and the efficacy of such an approach remains unestablished.

Although the use of epinephrine to increase blood glucose has been recommended in the past, this drug seldom is used today, largely because of its many systemic effects. Epinephrine increases hepatic glucose output via glycogenolysis and by decreasing peripheral glucose uptake, primarily in the muscle.

Glucagon is used rarely in the treatment of hyperinsulinemic hypoglycemia in neonates. This single-chain peptide, primarily secreted by the pancreatic alpha cells, increases blood glucose concentration by stimulating both glycogenolysis and gluconeogenesis. However, this effect is transient and variable. The most common use of glucagon in neonates is to diagnose hepatic glycogen storage disease, in which no or a minimal increase in blood glucose concentration is seen in response to glucagon.

Octreotide, a somatostatin analogue, can inhibit insulin secretion from the
pancreatic beta cells by activating a G-protein coupled-inward rectifier potassium channel and its subunits. Its short half-life (<3 min) and resultant short duration of action, however, have hampered its use in the treatment of neonates who have hyperinsulinemic hypoglycemia. Moreover, the possible inhibitory effects of octreotide on other hormones, such as growth hormone and thyrotropin, limit its usefulness.

References:


Content Specification(s):
Recognize the etiology, clinical manifestations, laboratory features, approach to therapy, and potential sequelae of neonatal hypoglycemia
You are called to the newborn nursery to evaluate an infant whose serum glucose concentration is less than 30 mg/dL (1.67 mmol/L) at 2 hours after birth. His birthweight was 4,250 g. On physical examination, you note macroglossia, visceromegaly, glabellar nevus simplex (salmon patch), and a large umbilical hernia.

Of the following, the MOST likely cause of hypoglycemia in this infant is:

1. abnormal fatty acid oxidation
2. adrenal insufficiency
3. islet cell hyperplasia
4. maternal diabetes
5. pancreatic adenoma

You selected 4, the correct answer is 3.

The combination of a birthweight that is greater than the 95th percentile, macroglossia, visceromegaly, glabellar nevus simplex, and large umbilical hernia or omphalocele reported for the infant in the vignette strongly suggests the diagnosis of Beckwith-Wiedemann syndrome (BWS). In BWS, neonatal hypoglycemia is due to pancreatic islet cell hyperplasia that results in hyperinsulinemia.

Hypoglycemia due to hyperinsulinemia in the newborn is reported most commonly in infants of diabetic mothers (IDMs). Although these babies are large for gestational age and have visceromegaly, there is usually a maternal history of diabetes, and the infants also may have polycythemia or hypocalcemia. IDMs generally do not have macroglossia or umbilical hernia/omphalocele. The hypoglycemia in both IDMs and infants who have BWS is due to islet cell hyperplasia.

Hyperinsulinemia appearing in the first year of life typically is associated with islet cell hyperplasia and may be transmitted as an autosomal recessive trait. Pancreatic adenomas, another cause of hyperinsulin-emia, generally occur in older children and adolescents. Abnormal fatty acid oxidation, adrenal insufficiency, and nesidioblastosis do not present with macroglossia, macrosomia, or umbilical hernia/omphalocele.

The primary goal of therapy for childhood hyperinsulinemia is to prevent the sequelae of hypoglycemia, including seizure disorder and mental retardation. For IDMs and those who have BWS, hyperinsulinemia usually is transient and requires the administration of intravenous dextrose to maintain normal serum glucose levels for only a few days. Children who have hyperinsulinemia due to pancreatic adenoma may require administration of glucocorticoids, diazoxide, dietary manipulation, and surgery in addition to glucose supplementation.

BWS is an overgrowth syndrome associated with molecular aberrations within the chromosome 11p15 region that have not yet been characterized fully. Once the neonatal metabolic derangements are treated and morphologic concerns are addressed, the prognosis is excellent.

References
Haymond MW. Hypoglycemia in infancy and childhood. In: Rudolph AM, Hoffman JIE,
Content Specification(s)
Recognize the etiology, clinical manifestations, laboratory features, approach to therapy, and potential sequelae of neonatal hypoglycemia
You are asked to see an 18-day-old female infant born at 32 weeks’ gestational age to a mother who had preterm labor and spontaneous vaginal delivery because the infant is not gaining weight despite adequate caloric intake. The family history is significant for an "overactive thyroid condition" in the father, paternal uncle, paternal grandfather, and male half-sibling. None of these individuals is receiving medication. Results of the initial state mandatory thyroid screen on the infant were normal. The mother denies a history of Graves disease or symptoms of hyperthyroidism and has no evidence of goiter or exophthalmos on physical examination. Thyroid function studies in the infant reveal elevated free and total thyroxine levels, normal concentrations of thyroid-stimulating hormone, negative screen for thyroid-stimulating immunoglobulins, and normal concentrations of thyroid-binding globulin.

Of the following, the MOST likely diagnosis in this infant is:

1. autosomal dominant hyperthyroidism
2. familial dysalbuminemic hyperthyroxinemia
3. neonatal Graves disease
4. thyroid hormone resistance
5. thyroxine-binding globulin excess

You selected 2, the correct answer is 4.

Thyroid disorders are the most prevalent endocrine disorders in the world, even more common than diabetes mellitus. Anatomic development of the hypothalamic-pituitary-thyroid system occurs during the first trimester of pregnancy, with significant concentrations of thyrotropin-releasing hormone (TRH) detectable by 15 to 18 weeks’ gestation. The human thyroid gland develops from the fourth pharyngobranchial pouch and the primitive pharyngeal floor. By 8 weeks' gestation, the thyroid gland has migrated to its definitive location in the anterior neck and by 10 weeks', all components necessary for function of the gland are present. Adequate quantities of iodide are essential for hormone synthesis, and during pregnancy the fetal thyroid gland competes with the maternal thyroid for available iodine sources. Because the placenta is impermeable to thyroid-stimulating hormone (TSH), the fetal hypothalamic-pituitary-thyroid system develops largely independently of the mother. Iodide and TRH readily cross the placenta, as do the thiourea drugs used to treat maternal Graves disease. Serum fetal TSH levels rise during the last half of pregnancy, influencing fetal thyroid gland function. Thyroid hormone production in the fetus is limited until 18 to 20 weeks' gestation, when thyroid follicular cell iodine uptake increases and serum thyroxine (T4) concentrations also begin to increase. Total and free T4 concentrations increase steadily until the final weeks of pregnancy. Delivery and resultant cold stress in the infant produce an acute release of TSH, which remains elevated for 3 to 5 days after birth. This elevation in TSH, in turn, causes triiodothyronine (T3) and T4 concentrations to rise after birth, peaking in the first few days after delivery. T3 and T4 decrease to normal infant levels by 4 to 5 weeks of age. Most of the circulating T3 after birth is derived from conversion of T4 to T3. Both T3 and T4 are associated with various plasma proteins, including thyroid-binding globulin (TBG) and albumin. These proteins serve as the primary transport proteins, with TBG binding approximately 60% to 70% of total T3 and T4.
A rare cause of hyperthyroxinemia in infants is thyroid hormone resistance. It is inherited as an autosomal dominant trait, with an incidence of approximately 1 in 100,000 births. Approximately 15% to 20% of cases appear sporadically. It is associated with deafness in 20% of affected patients and attention-deficit/hyperactivity disorder in 50% of patients. In generalized thyroid hormone resistance, patients can have elevated free T4 and T3 concentrations, with normal-to-increased TSH levels. Clinical manifestations may be those of mild hyperthyroidism. Nonsuppressed levels of TSH and absence of thyroid-stimulating immunoglobulins (TSIs) distinguish thyroid hormone resistance from Graves disease. When resistance of the circulating hormone is isolated to the pituitary gland, it is referred to as pituitary resistance to thyroid hormone syndrome. Coding genes for thyroid receptor proteins have been described on chromosomes 3 and 17. In all cases studied to date, the molecular defect involves the thyroid receptor beta-1 gene on chromosome 3. There is considerable variability of thyroid effects among family members who have identical mutations. The abnormal thyroid beta-receptor has minimal T3 binding and fails to mediate T3-regulated transcription. The affected male relatives, lack of maternal symptoms, absence of TSI, normal TSH concentration in the presence of elevated free T4, and mild symptoms described for the infant in this vignette suggest thyroid hormone resistance.

Autosomal dominant hyperthyroidism has been reported rarely. Most affected individuals have clinical manifestations during childhood or adolescence, occasionally during infancy, and rarely at birth. Hyperthyroidism with goiter, elevated total and free T4 levels, and suppressed TSH are the distinguishing features. Pathologic examination of the thyroid gland shows diffuse hyperplasia without lymphocytic infiltration. TSH receptor gene mutations have been characterized involving the third and seventh transmembrane segments of the TSH receptor, with mutated receptors demonstrating abnormally increased cyclic AMP-stimulating activity. TSI antibodies are absent, and the disorder is not transient. Therapy consists of short-term management with antithyroid drugs and partial thyroidectomy. The lack of clinical symptoms, including goiter and a normal TSH concentration, make autosomal dominant hyperthyroidism unlikely for the infant in the vignette.

Familial dysalbuminemic hyperthyroxinemia is the most common cause of inherited euthyroid hyperthyroxinemia in Caucasians. It occurs in approximately 1 in 10,000 newborns and is believed to be inherited as an autosomal dominant trait. Clinically, patients are euthyroid and have elevated serum T4 concentrations, but normal free T4 and TSH levels. The abnormality is a mutation in the albumin molecule resulting in increased T4 binding affinity. There is no clinical consequence to this disorder or therapy required. The elevated level of free T4 reported for the infant in the vignette obviates this diagnosis.

Hyperthyroidism in the newborn is rare and almost always is associated with maternal Graves disease. It is caused by transplacental passage of TSH receptor-stimulating antibodies, also known as TSIs. Maternal disease may be active or inactive. A substantial increase in concentration of TSI (in excess of 300% of control values) in cord blood or neonatal serum is associated with a high rate of neonatal Graves disease. Approximately 6% of infants born to mothers who have Graves disease exhibit mild-to-severe symptoms, such as irritability, tachycardia, hypertension, hyperkinesia, poor weight gain, vomiting, and diarrhea, and in severe cases, cardiac failure and death. Laboratory analysis may reveal thrombocytopenia, jaundice, and advanced bone age. Craniosynostosis is seen in severe cases. Physical examination may document goiter, exophthalmos, arrhythmias, and hepatosplenomegaly. An elevated free T4 concentration, absent or low level of TSH, and presence of TSI confirm the diagnosis. The course of illness is self-limited because of the gradual depletion of the antibody over the first few weeks after birth. The half-life of TSI is approximately 12 days, and the usual clinical course lasts from 3 to 12 weeks. Treatment of hyperthyroidism in the newborn consists of iodine (Lugol's) solution and an antithyroid drug, usually propylthiouracil. Adjunctive
therapy may include a beta-adrenergic blocking agent to alleviate serious symptoms as well as the use of digitalis for cardiac failure and occasionally hydrocortisone as an anti-inflammatory agent. Medications are tapered as TSI levels decrease and the infant becomes less symptomatic.

In some cases of maternal Graves disease, the TSH receptor-blocking antibodies may pass transplacentally, resulting in clinical hypothyroidism in the infant at birth. When maternal Graves disease is treated with antithyroid medication that crosses the placenta, an initial hypothyroid state in the infant evolves into hyperthyroidism as the medication dissipates. Hyperthyroid symptoms may not occur until 5 to 14 days after birth. Due to these different clinical presentations, thyroid function in infants of mothers who have Graves disease must be monitored closely in the first postnatal weeks. The infant in the vignette has absent TSI, normal TSH concentrations, a negative maternal history, and a lack of symptoms, which makes neonatal Graves disease unlikely.

Thyroid-binding globulin excess occurs in 1 in 6,000 to 40,000 newborns. Total T4 levels are elevated due to the increased binding capacity of the TBG that is present, but free T4 and TSH levels are normal, and the infant is euthyroid. The mechanism of this disorder is increased TBG production by the liver, with levels up to 4.5 times normal. Review of available data suggests an X-linked mode of inheritance. The elevated free T4 and inheritance pattern described in the vignette do not suggest TBG excess.

References:


Content Specifications:

Understand the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction

Identify the etiology and clinical manifestations of congenital hyperthyroidism

Know the laboratory features and treatment of congenital hyperthyroidism
A newborn has ambiguous genitalia characterized by posterior fusion of the labioscrotal folds and clitoromegaly. Findings include: chromosome analysis, a normal female 46,XX pattern; sodium, 127 mEq/L; potassium, 6.5 mEq/L; markedly increased levels of 17-hydroxyprogesterone and androstenedione. You diagnose the salt-wasting form of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency.

When discussing options for future pregnancies, the MOST appropriate statement to include is that

- CAH is identified best by measurement of amniotic fluid 17-hydroxyprogesterone
- prenatal diagnosis of CAH can be determined by molecular analysis of fetal DNA
- the fetal gender should be determined by ultrasonography because only females are at risk
- the mother should receive dexamethasone therapy throughout all future pregnancies
- there is a 50% risk for an affected child in each future pregnancy

You selected 3, the correct answer is 2.

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that results from deficiency of the enzyme 21-hydroxylase. The gene for this enzyme has been identified, and it is now possible to determine the exact molecular defect(s) in most families, which permits precise prenatal diagnosis by examination of fetal DNA obtained by chorionic villus sampling or amniocentesis. To facilitate such studies, the affected child and both parents should undergo genetic counseling and molecular genotyping of the 21-hydroxylase gene prior to initiating another pregnancy. In addition, couples at risk should be advised that early detection in all future pregnancies is necessary to prevent or minimize the virilizing effects on affected female fetuses.

CAH occurs as two distinct phenotypes: a simple virilizing form (25% to 33% of patients) and a salt-wasting form (67% to 75% of patients). In both forms, the deficiency of 21-hydroxylase results in decreased cortisol synthesis by the adrenal gland and the increased production of cortisol precursors (eg, 17-hydroxyprogesterone) and androgens, which do not require 21-hydroxylase for their synthesis. Because fetal genital development is regulated by adrenal steroid synthesis, the presence of elevated androgen levels in affected female fetuses results in variable degrees of virilization. In the salt-wasting form of the disease, renal salt wasting due to deficient aldosterone synthesis also occurs. The degree of virilization in affected females is not predictive of salt wasting, and even those who have mild virilization must be monitored for this possibility. However, the presence or absence of salt wasting usually is consistent in affected members of the same family. Thus, for the family described in the clinical vignette, any future affected infants also would be expected to have the salt-wasting form of CAH.

The management goals for pregnancies at risk for CAH are to identify affected fetuses of both sexes and to minimize virilization in affected females. To achieve these goals, oral dexamethasone therapy must be initiated as soon as the pregnancy is detected. This semisynthetic steroid can cross the placenta and suppress the fetal adrenal gland in affected female fetuses, thereby minimizing the virilizing effects. Fetal cells then are obtained either by chorionic villus sampling at 10 weeks'
gestation or by amniocentesis at 15 to 18 weeks' gestation. DNA from these cells then is used to determine the fetal sex by chromosome analysis and for molecular testing (ie, 21-hydroxylase genotyping) to determine the disease status. If a male fetus is identified by the chromosome analysis, the dexamethasone can be discontinued. If the fetus is identified as female, the dexamethasone is discontinued only if results of the molecular analysis reveal that the fetus is unaffected. For pregnancies involving affected female fetuses, treatment is continued until delivery. All infants should be tested at birth to confirm the prenatal diagnosis by measuring 17-hydroxyprogesterone levels and repeating molecular analysis. Infants who were identified as affected by the prenatal testing also should have electrolyte levels measured on the first and second day of life to monitor for the salt-wasting form of CAH.

Prior to the availability of molecular testing, determination of 17-hydroxyprogesterone levels in amniotic fluid was used to identify fetuses who had CAH. Although 17-hydroxyprogesterone levels clearly are elevated in the severe salt-wasting form of CAH, they may be normal in the simple virilizing form. Thus, this method lacks sensitivity and has been replaced by molecular testing for those families in which the mutation has been identified. Although ultrasonographic determination of fetal sex is possible, the prenatal management of CAH requires precise determination of the sex of the fetus, which is achieved best by fetal cell sampling and chromosome analysis. Because CAH is inherited as an autosomal recessive trait, the risk for an affected infant in each pregnancy is 25%.

References:

Content Specification(s)
Know the etiology and diagnosis of an infant with ambiguous genitalia, including congenital adrenal hyperplasia
A 3-day-old infant has been refusing to feed and is becoming increasingly lethargic. An evaluation for sepsis, including a complete blood count and cultures of blood, urine, and cerebrospinal fluid, is performed, and antibiotic therapy is initiated while awaiting the culture results.

Of the following, the MOST appropriate additional laboratory test to obtain now is

- plasma very long-chain fatty acids
- serum ammonia level
- stool porphyrin levels
- total and direct serum bilirubin concentrations
- urine mucopolysaccharide concentration

You selected 3, the correct answer is 2.

The preferred response is 2. serum ammonia level.

Acute illness in the neonate typically is characterized by nonspecific symptoms, regardless of the underlying etiology. Symptoms may include alterations in tone, suck, feeding, and respirations as well as lethargy. The refusal to feed and increasing lethargy described for the infant in the vignette should prompt an evaluation directed at identifying either an infectious or metabolic cause of the symptoms. Investigations should be conducted concurrently because delay in diagnosing an inborn error of metabolism can result in substantial neurologic damage that may be permanent.

In particular, the deterioration of a previously well neonate suggests an intoxication type of metabolic disorder. These problems typically present with poor suck and feeding followed by increasing lethargy and coma. The most common ones are the organic acidemias, maple syrup urine disease, urea cycle defects, and nonketotic hyperglycinemia. Once a metabolic disorder is suspected, laboratory testing should be conducted immediately to aid in the precise diagnosis and to permit appropriate intervention. Ammonia and lactic acid levels, tests that are readily available in most hospital laboratories, should be measured immediately to guide the subsequent evaluation. Serum amino acid and urine organic acid analyses, which many hospitals refer to specialty laboratories, also should be initiated. Hyperammonemia with ketoacidosis is highly suggestive of an organic acidemia, and the precise diagnosis will be confirmed by analysis of organic acids. Some organic acidemias also result in granulocytopenia and thrombocytopenia, laboratory findings that frequently are mistaken for sepsis. This mistaken diagnosis can delay the further evaluation of affected infants whose clinical condition will continue to deteriorate despite broad-spectrum antibiotic therapy. Alternatively, hyperammonemia with respiratory alkalosis is more suggestive of a urea cycle defect, a diagnosis that can be confirmed either by detection of a typical pattern of amino acid abnormalities or by demonstration of the specific enzymatic deficiency in a liver biopsy specimen.

Stool porphyrin levels are useful in the diagnosis of the porphyrias, which are inherited defects of porphyrin metabolism. However, most of these disorders present later in life with cutaneous symptoms or abdominal pain. Determination of urine mucopolysaccharide concentrations is helpful in the initial evaluation of a child.
suspected of having a mucopolysaccharidosis. These disorders typically present later in infancy with coarse facial features, organomegaly, and developmental delay. Definitive diagnosis following suggestive findings on the urine test requires demonstration of the specific enzymatic deficiency in peripheral blood leukocytes or cultured fibroblasts.

Total and direct serum bilirubin concentrations may be obtained as part of the evaluation of a sick infant, but this result would not be specific enough to lead to the correct diagnosis. Very long-chain fatty acid levels are elevated in infants and children who have peroxisomal disorders. In the newborn period such conditions include Zellweger syndrome, but this disorder is characterized by dysmorphic facial features, hepatomegaly, and profound hypotonia that is evident from birth.

References:


Content Specification(s):

Recognize and diagnose the metabolic disorders that lead to coma

PREP 2000  SA # 137
You are discussing with a medical student the factors affecting the energy requirements of a preterm neonate.

Of the following, the MOST accurate statement about energy expenditure of a preterm infant is that:

- a thermoneutral environment is effective in minimizing energy expenditure
- diet-induced thermogenesis is higher with continuous than with intermittent feeding
- metabolic cost of growth is higher with deposition of fat than with synthesis of protein
- physical activity is the major component of total energy expenditure
- resting metabolic rate decreases with advancing postnatal age

You selected 3, the correct answer is 1.

The preterm neonate's energy expenditure can be minimized by keeping the infant in a thermoneutral environment. A thermoneutral environment is a range of ambient temperatures within which the metabolic rate of the infant is minimal and the infant can maintain a normal body temperature without any regulatory changes in metabolic heat production or evaporative heat loss. The thermoneutral range varies with gestational age. In an unclothed resting adult, the lower limit of the thermoneutral range is 26°C to 28°C (78.8°F to 82.4°F) in an environment of 50% relative humidity and still air. Under similar conditions, the lower limit of the thermoneutral range is 32°C (89.6°F) or higher in a naked term neonate and 35°C (95°F) or higher in a naked preterm neonate.

Diet-induced thermogenesis, also known as specific dynamic action, thermic effect of food, or postprandial thermogenesis, is the increase in metabolic rate that follows food intake. It represents the energy consumption necessary for digestion, absorption, and assimilation of nutrients. The magnitude of increase in energy expenditure following the ingestion of nutrients is estimated to vary between 4% and 30% in both term and preterm neonates. Diet-induced thermogenesis is lower with continuous than with intermittent enteral feeding.

Metabolic cost of growth represents the energy required for the formation of new tissue, and it varies with the composition of the synthesized tissue. The cost of depositing absorbed dietary fat into adipose tissue is much less than that of synthesizing new protein. The overall metabolic cost of growth in neonates is estimated at approximately 4.4 kcal/g of weight gain.

Energy expenditure increases with physical activity, but because neonates sleep 80% to 90% of the time, physical activity is a small component of their energy expenditure compared with that of adults. It is estimated that physical activity contributes to only about 10% of the total energy expenditure in preterm neonates.

Resting metabolic rate increases steadily from birth in both term and preterm neonates. The resting metabolic rate in term neonates is estimated at approximately 40 kcal/kg per day at 3 days of postnatal age, increasing to approximately 60 kcal/kg per day at 3 months of postnatal age. A similar but smaller increase in resting metabolic rate is observed in preterm neonates.
References:


Content Specification(s):

Understand the coloric cost of physical activity.

Understand the caloric cost of maintaining body temperature.
A 2-week-old infant is admitted to the hospital due to poor feeding, intermittent vomiting, and lethargy. He is evaluated for sepsis, oral feedings are stopped, and he is given maintenance intravenous fluids and antibiotics. After 3 days, all culture results are negative, and the baby is alert. Feedings are restarted using a cow milk formula, and 2 days later the baby is obtunded. Results of laboratory tests show metabolic acidosis with elevated anion gap, elevated lactate, mild hypoglycemia, hyperammonemia, and neutropenia.

Of the following, the MOST likely diagnosis is:

1. argininosuccinic aciduria
2. galactosemia
3. maple syrup urine disease
4. medium-chain acyl-CoA dehydrogenase deficiency
5. methylmalonic acidemia

You selected 2, the correct answer is 5.

Neonatal lethargy that progresses to coma and is associated with vomiting is caused by an inborn error of metabolism until proven otherwise. Progressive lethargy often is associated with an elevated ammonia level, especially in the context of improved alertness when protein administration is withdrawn, as described for the infant in the vignette.

The differential diagnosis of infantile hyperammonemia is extensive, but it can be divided into two major categories: conditions with and without metabolic acidosis. The latter group includes argininosuccinic aciduria and the urea cycle disorders; the former group includes the organic acidemias and fatty acid oxidation defects, of which medium chain acyl-CoA dehydrogenase deficiency (MCADD) is the most common. MCADD typically presents at about 4 months of age or when the infant starts to sleep through the night. Maple syrup urine disease usually presents in the first days of life with progressive lethargy and seizures. It is not associated with hyperammonemia or acidosis. Galactosemia could present at this age and with similar symptoms to those of the child in the vignette, but it is not associated with elevated serum ammonia or lactate. Accordingly, organic acidemia is the most likely diagnosis for the infant described in the vignette.

Of the organic acidemias, propionic acidemia and methylmalonic acidemia both present with vomiting, lethargy, metabolic acidosis with increased anion gap, and elevated serum ammonia levels. Both conditions are due to the impaired breakdown of a number of amino acids. Accumulation of toxic intermediates interferes with urea cycle function, resulting in elevated ammonia levels. Acidosis is caused by elevated lactic and keto-acids, which impede normal bone marrow function.

Management of propionic acidemia and methylmalonic acidemia is aimed at limiting protein intake while providing sufficient calories to promote growth. Carnitine supplementation is an important adjunctive therapy that allows for formation of acylcarnitines and prevention of secondary carnitine deficiency. It may be necessary to administer blood products during crises.
References:

Content Specification(s):
Understand the clinical manifestations, laboratory features, and treatment of metabolic disorders including disorders in the metabolism of amino acids, fatty acids, organic acids, the urea cycle, and carbohydrates (excluding glucose), and cholesterol synthesis
An infant born at term appears healthy. The mother expresses a wish to breastfeed. You take a maternal history and review her records.

Of the following, the condition that is an ABSOLUTE contraindication to ingestion of human milk or breastfeeding is:

- galactosemia
- maternal human immunodeficiency virus positivity
- maternal tuberculosis
- maternal vaginal herpes
- phenylketonuria

You selected 2, the correct answer is 1.

Infants who have galactosemia lack activity of the galactose-1-phosphate uridyl transferase (GALT) enzyme and are unable to interconvert galactose (a component of lactose) to glucose. Therefore, human milk and all lactose-containing foods are contraindicated for affected infants. Soy-based formula feeding should be initiated immediately on diagnosis. Clinically untreated infants experience difficulty in feeding and failure to thrive and exhibit hepatosplenomegaly, prolonged jaundice, galactosuria, and albuminuria. Infants who have galactosemia may have cataracts, and they have increased susceptibility to *Escherichia coli* sepsis. Although most galactose-glucose interconversion occurs in the liver, GALT activity is needed in other tissues, and the lack of interconversion can result in accumulation of galactose-1-phosphate. After ingestion of lactose, affected individuals’ red blood cells accumulate galactose-1-phosphate. Testing of red blood cells for GALT activity can detect the condition. Enzyme assay of fetal cells from chorionic villus or amniotic fluid sampling can be used for prenatal diagnosis. The GALT gene has been identified, cloned, and sequenced, and several mutations have been identified. The condition has an autosomal recessive inheritance pattern. Although early treatment with a nonlactose-containing diet may be lifesaving, long-term intellectual and language problems may persist.

Whether maternal human immunodeficiency virus (HIV) infection is a contraindication to breastfeeding depends on the availability of clean water and the risk of enteric infections. In the United States, HIV infection is considered a contraindication to breastfeeding because the HIV virus is excreted in maternal milk. In some underdeveloped countries, however, the benefits of breastfeeding may exceed the risk for acquisition of HIV through the milk.

A mother who has active infectious tuberculosis may not breastfeed until she is treated adequately. Once the mother has received 2 weeks of effective antibiotic therapy, she no longer is considered infectious, and breastfeeding may be introduced.

Vaginal herpes infection is not a contraindication to breastfeeding unless herpetic lesions also are present on the breast.

Infants who have phenylketonuria require careful regimentation of their dietary protein intake, but they do need some whole protein in the diet, which may be provided through human milk. Due to the complexity of the phenylketonuria diet, use
of human milk may be complicated, but it is not contraindicated.

References


Content Specifications
Realize the problems associated with breast feeding

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of carbohydrates (excluding glucose)
A newborn presents with gastroschisis. You anticipate the need for prolonged total parenteral nutrition. The nurses inquire about the need for trace mineral supplementation.

Of the following, the trace mineral that requires the EARLIEST supplementation is

- chromium
- copper
- manganese
- selenium
- zinc

You selected 2, the correct answer is 5.

Nine trace elements have been identified as having practical importance in human nutrition: copper, chromium, fluoride, iodine, iron, manganese, molybdenum, selenium, and zinc. Newborns receiving prolonged total parenteral nutrition have the potential for deficiency of these elements.

Zinc should be supplemented at the onset of total parenteral nutrition because deficiency of this mineral can develop rapidly. The dose of zinc is determined by weight, growth rate, gestational age, and chronologic age of the infant. The dosage may need to be raised in the presence of increased urinary output (eg, high-output renal failure) or gastrointestinal output (eg, high stool volume or losses through ostomies). Clinical zinc deficiency is characterized by an erythematous rash of the perioral, perineal, and facial areas, although biochemical evidence precedes the appearance of clinical symptoms. The diagnosis is confirmed by measuring plasma concentrations of zinc. Low plasma concentrations of alkaline phosphatase should raise suspicion for zinc deficiency.

Supplementation with chromium, copper, manganese, or selenium is not required until after 4 weeks of parenteral nutrition.

Copper deficiency may be seen among preterm infants due to low stores and rapid growth. Clinical features of copper deficiency include a hypochromic anemia unresponsive to iron, osteoporosis, and neutropenia. The diagnosis can be confirmed by low plasma concentrations of copper or by decreased concentrations of the enzyme copper, zinc-superoxide dismutase in erythrocytes. Increased doses are necessary in the presence of biliary losses (eg, jejunostomy or biliary fistula) because copper is stored in the liver and excreted in the bile. Supplementation should be avoided in the presence of cholestasis.

Manganese plays a role in gluconeogenesis, protects mitochondrial membranes, and activates glycosyl transferase as a part of mucopolysaccharide synthesis. A neonatal deficiency syndrome has not been described, probably because magnesium can replace the role of manganese. Withholding manganese supplementation has been suggested in the presence of cholestasis. Protracted high plasma concentrations of manganese can result in deposition in the brain, resulting in memory loss, weakness, and an extrapyramidal syndrome.

Chromium plays a role in glucose uptake, but no clinical deficiency syndrome has
been described. Little is known about chromium in parenteral nutrition for neonates; recommended doses for neonates are based on adult data. Chromium accumulation can occur in the presence of renal dysfunction because it is excreted in the urine.

Selenium deficiency has been reported with long-term parenteral nutrition. Affected patients show cardiac and skeletal myopathy, decreased skin and hair pigmentation, and erythrocyte macrocytosis. Biochemical markers of selenium deficiency include low plasma concentrations of selenium and reduced glutathione peroxidase activity. Selenium accumulation can occur in the presence of renal dysfunction because it is excreted in the urine.

References:

Content Specification(s):
Understand the clinical manifestations and diagnosis of zinc deficiency
Understand the management and prevention of zinc deficiency
Recognize the clinical manifestations and diagnosis of copper deficiency
Understand the management and prevention of copper deficiency
Understand the clinical manifestations and diagnosis of selenium deficiency
Understand the management and prevention of selenium deficiency
Understand the clinical manifestations and diagnosis of manganese deficiency
Understand the management and prevention of manganese deficiency
Understand the clinical manifestations and diagnosis of chromium deficiency
A 45-day-old female infant, whose estimated gestational age at birth was 25 weeks and birthweight was 650 g, has clinical and radiographic evidence of bronchopulmonary dysplasia. She is receiving exclusively parenteral nutrition following an episode of necrotizing enterocolitis. An error was made in the prescription of her parenteral nutrition solution that has resulted in administration of the vitamin supplement at 50 times the intended dose.

Of the following, the MOST likely cause of acute toxicity in this infant is excess vitamin A.

Both excesses and deficiencies of vitamins can pose risks to the parenterally fed infant. The infant described in the vignette is at the highest risk for toxicity of vitamin A (retinol). The recommended vitamin A dose for parenterally fed preterm infants is 700 to 1,500 mcg/kg per day, which is increased to 1,500 to 2,800 mcg/kg per day when lung disease is present. The acute form of hypervitaminosis A may result from a single large dose of vitamin A in excess of 100,000 IU. The primary complication of acute hypervitaminosis A is increased intracranial pressure. Chronic hypervitaminosis A may result from prolonged receipt of vitamin A in excess of 25,000 IU per day. In addition to symptoms and signs of increased intracranial pressure, the clinical manifestations of chronic hypervitaminosis A include bone and joint pains, mucocutaneous lesions, and hepatomegaly. Laboratory studies may document hepatotoxicity, hypercalceemia, and hematologic abnormalities. The plasma vitamin A concentration in vitamin A toxicity generally exceeds 100 mcg/dL (3.5 mcmol/L), and the ratio of retinyl ester (storage form of vitamin A) to free retinol (vitamin A alcohol) is increased in the presence of usually normal retinol-binding protein, the carrier protein of vitamin A. Skeletal radiography may show widened metaphyses in the distal ulna and hyperlucent zones in the radius. Cortical hyperostosis and soft-tissue calcifications may be seen in children older than 6 months of age.

The daily recommended dose of vitamin C (ascorbic acid) for preterm infants is 25 to 31 mg/kg. Adults and older children can clear large amounts of vitamin C, but preterm infants may accumulate ascorbic acid, which poses a theoretical risk of elevated urinary oxalate and uric acid. However, no acute toxic syndrome associated with vitamin C has been identified.

Vitamin D status can be maintained by parenteral supplementation. Normal vitamin D status may be maintained for infants receiving dextrose/amino acid solutions by supplementing with vitamin D at 30 IU/kg per day (maximum, 400 IU per day) and for infants receiving lipid emulsions by supplementing with vitamin D at 160 IU/kg per day (maximum, 400 IU per day). Hypervitaminosis D may result from a single large dose of vitamin D in excess of 10,000 IU or from prolonged exposure to vitamin D in excess of 4,000 IU per day. The clinical manifestations of hypervitaminosis D include
nausea, vomiting, polyuria, and failure to thrive. Laboratory studies may show hypercalcemia and hypercalcuria. Radiographic studies may indicate ectopic calcifications.

Toxicity has been reported in preterm infants in conjunction with the use of an intravenous vitamin E-polysorbate preparation. These infants had respiratory deterioration, thrombocytopenia, liver failure, and renal failure, and in many instances, the outcome was fatal. The toxicity was attributed to polysorbate used in the solution as a stabilizer rather than vitamin E itself. Nevertheless, vitamin E cannot be considered innocuous. Preterm infants receiving tocopherol orally and parenterally may be at increased risk for sepsis and necrotizing enterocolitis. However, no acute toxic syndrome associated with vitamin E has been described. The recommended dose of vitamin E for parenterally fed infants is 3.5 mg/kg per day.

Vitamin K long has been given to infants to prevent hemorrhagic disease of the newborn. An early formulation of vitamin K, menadione, was associated with hemolysis and interference with protein binding of bilirubin. No known toxicity is seen with currently used forms of vitamin K, and no "hypervitaminosis K" has been described. The recommended dose for parenterally fed infants is 8 to 10 mcg/kg per day.

References:


Content specification(s):

2395. Understand the clinical and laboratory manifestations of excesses of fat-soluble vitamins
A 3-day-old infant presents to the emergency department with vomiting, lethargy, hypotonia, and jaundice. Physical examination reveals hepatomegaly and neurologic depression. A full sepsis evaluation is undertaken, and the Gram stain of the cerebrospinal fluid reveals gram-negative organisms.

Of the following, the BEST additional laboratory test to obtain is

1. erythrocyte galactose-1-phosphate
2. liver glycogen content
3. plasma insulin level
4. plasma very long-chain fatty acids
5. stool porphyrins

You selected 3, the correct answer is 1.

The combination of vomiting, lethargy, neurologic depression, jaundice, hepatomegaly, and gram-negative sepsis in an infant is highly suggestive of galactosemia. This condition results from deficiency of the enzymatic activity of galactose-1-phosphate uridylyltransferase and the subsequent inability to metabolize galactose. The diagnosis can be confirmed by direct measurement of the enzyme in erythrocytes and quantitation of erythrocyte galactose-1-phosphate.

The clinical course of galactosemia in affected infants can be fulminant, which has led to its inclusion in the newborn screening programs of some states. Untreated patients suffer an early demise or have mental retardation if they survive. Treatment includes restriction of galactose from the diet, although affected infants typically require additional forms of therapy to correct the hyperbilirubinemia. Unless appropriate dietary therapy is initiated, the clinical response to antibiotic therapy in infants who have gram-negative sepsis may be poor.

Parents of affected infants should be counseled about the recurrence risk in future pregnancies because the disorder is inherited as an autosomal recessive trait. The recurrence risk is 25%, and prenatal diagnosis is available.

The glycogen storage diseases that are accompanied by hepatomegaly usually present later in infancy and are not associated with gram-negative infections. Hyperinsulinemia usually presents with hypoglycemia, which may manifest as a seizure in the neonatal period. Hepatomegaly and sepsis are not associated features. Plasma long-chain fatty acids are elevated in the peroxisomal disorders. Among these, Zellweger syndrome can present at birth with profound hypotonia, dysmorphic features, hepatomegaly, and congenital cataracts. Sepsis and presentation after the immediate newborn period are not typical. Stool porphyrin measurement is useful in the diagnosis of the porphyrias, which typically present later in childhood and are not characterized by severe illness in infancy.

References:
Content specifications(s):
Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of carbohydrates (excluding glucose)
You are notified by the newborn screening program that a 2-week-old infant in your practice has an elevated phenylalanine level, which is confirmed by repeat testing. The mother reports that the baby is healthy and breastfeeding well.

Of the following, the MOST important first step in management of this infant is to

<table>
<thead>
<tr>
<th></th>
<th>admit the baby to the hospital for further evaluation</th>
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<tbody>
<tr>
<td>2</td>
<td>consult with a metabolic geneticist or nutritionist</td>
</tr>
<tr>
<td>3</td>
<td>instruct the mother that she no longer should breastfeed</td>
</tr>
<tr>
<td>4</td>
<td>place the baby immediately on phenylalanine-free formula</td>
</tr>
<tr>
<td>5</td>
<td>send urine for organic acid analysis</td>
</tr>
</tbody>
</table>

You selected 5, the correct answer is 2.

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism that has an incidence of approximately 1:10,000 to 1:25,000 individuals. The gene that causes PKU is well described and is mapped to chromosome 12 on the long arm. More than 240 mutations causing PKU have been defined, and carrier detection and prenatal diagnosis are available using molecular genetic testing.

Newborn screening programs for PKU initially were established based on the discovery that the early diagnosis and treatment of the disease virtually could eliminate morbidity and mortality. An elevated blood phenylalanine (PHE) concentration detected by newborn screening performed after the initiation of feeding, as described for the infant in the vignette, suggests the need for a diagnostic evaluation. However, it is important to realize that most infants in whom elevated PHE levels are identified through screening programs do not have PKU; they simply have delayed maturation of the metabolizing enzymes. Individuals who have classic PKU and continue to feed normally experience a rapid rise in serum PHE concentration to levels greater than 30 mg/dL (1,815 mcмол/L) (normal, 1 mg/dL [60.5 mcмол/L]). Some individuals have a variant termed “hyperphenylalaninemia,” which also results from defective phenylalanine hydroxylase. Yet another group of individuals has biopterin deficiency; biopterin serves as a cofactor (in the form of tetrahydrobiopterin) for the formation of tyrosine from PHE.

Following the identification of an infant who has a positive newborn screening result for PKU, the most efficient next step is either to repeat the screening test or to send blood for amino acid quantitation. Because such test results are seen infrequently in general pediatric practices, it is important to consult with a metabolic geneticist. The results of the amino acid analysis allow the geneticist to distinguish among true PKU, in which the PHE level is very elevated and the tyrosine level is negligible; hyperphenylalaninemia, in which the level is elevated in the intermediate range (10 to 20 mg/dL [605 to 1,210 mcмол/L]) and there may be some tyrosine; and newborn immaturity in which the PHE level is elevated, but there is sufficient tyrosine. It is not necessary to admit the baby in the vignette to the hospital at this juncture because he is stable and is not expected to decompensate. If the mother discontinues breastfeeding and the baby does not have PKU, the opportunity to breastfeed may be lost. Phenylalanine-free formula is expensive, and 2 to 3 days of therapy while awaiting test results has no clear advantage. Finally, urine organic acid analysis is not helpful.

Once the diagnosis of PKU is confirmed, it is critical to confer with a metabolic geneticist/nutritionist and, if at all possible, to have the patient seen at a metabolic clinic.
Therapy involves restriction of dietary PHE to the amount tolerated by the patient and regular measurement of plasma PHE concentrations. It also is important to follow plasma tyrosine concentrations because tyrosine becomes an essential amino acid in affected children.

When carefully managed and followed, individuals who have PKU have a very bright prognosis, both for health and for cognitive function. It is important to note that years ago, children were taken off their special diets at about the age of 6 years. However, it now appears best to keep affected individuals on their diets indefinitely because of measurable declines in intelligence quotient and school performance in individuals who came off the diet. Additionally, due to the potential for the severe negative impact of hyperphenylalaninemia on the embryos and fetuses of affected women, it is best to continue the diet throughout life.

References:


Content Specifications: Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids
A 3,200-g term male infant presents for his 1-week evaluation. The pregnancy and delivery were uneventful. His parents state that the baby has been difficult to arouse, is feeding poorly, and has been vomiting. On physical examination, the infant weighs 2,800 g, is lethargic and jaundiced, and has a palpable liver 3 cm below the right costal margin. An evaluation for sepsis has been performed and antibiotic therapy initiated. Additional laboratory results include: total bilirubin, 18 mg/dL (307.8 mcmol/L); direct bilirubin, 6 mg/dL (102.6 mcmol/L); alanine aminotransferase, 104 U/L; aspartate aminotransferase, 150 U/L; and positive urine dipstick for protein and reducing substances.

Of the following, the test that would be MOST helpful in the diagnosis of this patient is

- Coombs test and maternal anti-Rh titer
- Examination of a blood smear for red cell morphology
- Serum amino acids and urine organic acids
- Serum galactose-1-phosphate uridylyltransferase level
- Serum hepatitis B surface antigen

You selected 1, the correct answer is 1.

Direct or conjugated hyperbilirubinemia in the neonatal period may result from intrinsic liver disease or a congenital hepatobiliary obstruction. In these cases, conjugated bilirubin levels increase rapidly during the first few postnatal weeks to greater than 2 mg/dL (34.2 mcmol/L) and remain elevated. Underlying causes include bacterial or viral sepsis, nonspecific neonatal hepatitis, galactosemia and other metabolic disorders (tyrosinemia, fructosemia, Niemann-Pick disease, Gaucher disease, glycogenosis Type IV, cystic fibrosis), severe hemolysis (with inspissation of bile, which may be seen in Rh disease), biliary atresia, extrahepatic biliary obstruction, alpha-1-antitrypsin deficiency, isolated defects in hepatic bilirubin transport, and neonatal hemosiderosis. A prompt investigation should be undertaken to determine the cause of the conjugated hyperbilirubinemia because some of the causative conditions may be serious and life-threatening and have significant implications for the child’s health and future development.

The symptoms exhibited by the infant described in the vignette, coupled with their time of onset and the presence of reducing substances in the urine, suggest the diagnosis of galactosemia. Therefore, measurement of the serum galactose-1-phosphate uridylyltransferase level would be the most helpful. Obtaining a Coombs test and maternal anti-Rh titer, serum amino acids and urine organic acids measurements, and a peripheral blood smear is appropriate for the evaluation of an infant who has unconjugated hyperbilirubinemia. Hepatitis B virus infection may cause conjugated hyperbilirubinemia, but the patient's age and clinical presentation are not consistent with neonatal hepatitis B infection.

References:

Abstract available online

**Abstract available online**

**Content specifications:**
- Understand the differential diagnosis, evaluation, and approach to management of mixed forms of jaundice.
- Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of carbohydrates (excluding glucose).
You are caring for a 7-week-old infant born at 23 weeks postconceptional age whose birthweight was 540 g. Her early course was complicated by severe respiratory failure, candidal sepsis, and multiple episodes of feeding intolerance as well as suspected necrotizing enterocolitis. She received parenteral nutrition until 40 days after birth, when full enteral nutrition was established with maternal breast milk. A chest and abdominal radiograph revealed the ribs to be osteopenic, with new fractures of the fifth and sixth thoracic ribs and bilateral healing femoral fractures. Laboratory results show: serum calcium of 10.1 mg/dL (2.5 mmol/L), alkaline phosphatase of 823 U/L, and serum phosphorus of 4.2 mg/dL (1.4 mmol/L).

Of the following, the MOST appropriate initial nutritional supplement for this infant is

1. calcium gluconate
2. human milk fortifier
3. multivitamin supplement
4. potassium phosphate
5. vitamin D

You selected 1, the correct answer is 2.

Osteopenia of prematurity, also referred to as metabolic bone disease or neonatal rickets, affects up to 30% of infants whose birthweights are less than 1,500 g; the incidence is inversely proportional to birthweight. Some 73% of infants whose birthweights are less than 800 g have abnormalities documented on bone radiographs. The severity ranges from mild demineralization to overt rickets and nontraumatic fractures. Calcium (Ca) and phosphorous (P) are the major inorganic constituents of bone. After 24 weeks’ gestation, fetal accretion of Ca is 92 to 150 mg/kg per day and P is 59 to 85 mg/kg per day. Preterm infants miss this period of substantial mineral accretion such that an infant born at 24 weeks’ gestation has only 10% to 15% of total body Ca compared with a term neonate. Other predisposing factors for osteopenia of prematurity are outlined in Table 1.

Osteopenia of prematurity is clinically asymptomatic in most cases, with radiographic changes appearing between the 6th and 12th postnatal weeks. Fractures are seen most commonly in the thoracic cage and extremities. Respiratory distress may ensue, caused by softening of the ribs and poor chest wall compliance. Craniotabes, frontal bossing, and palpable costochondral junctions (rachitic rosary) may be physical findings in more severe and prolonged cases.

The typical biochemical features of osteopenia of prematurity include a normal serum Ca concentration, low serum P level, and high serum alkaline phosphatase concentration (generally more than five times the upper adult normal reference values), as reported for the infant in the vignette. Urinary excretion of P is low or absent, and urinary Ca excretion increases as serum P concentrations decline, which suggests that P is the limiting nutrient. Serum 1,25-dihydroxyvitamin D levels are elevated, as would be expected, and return to normal with mineral supplementation, which makes this a useful marker for adequate therapy. Hyperparathyroidism typically is not present. Dual energy x-ray absorptiometry (DEXA) is the standard for whole body mineral evaluation, but the lack of portable DEXA scanning makes a plain radiograph of the wrist or humerus a practical screening tool. However, bone mineral content must decrease by 30% to 40% to appreciate changes on plain radiography.

Osteopenia of prematurity appears to be caused by insufficient provision of Ca and P rather than inadequate absorption in the gastrointestinal tract. It is difficult to attain accretion rates of
Ca and P similar to those seen in the fetus with parenteral nutrition because of limited solubility of the Ca and P salts and the high concentrations recommended (60 to 90 mg/kg per day of Ca, 47 to 70 mg/kg per day of P). Human milk is an insufficient source of Ca and P for the preterm infant, providing approximately one half to two thirds of the recommended intake. Human milk fortifier or premature infant formulas provide both additional Ca and P and represent the first step in nutritional supplementation to avoid or correct osteopenia. In some cases, even this is inadequate to correct P deficiency, and additional P supplementation is needed. For the infant in the vignette, who is being fed unfortified human milk, human milk fortifier can provide additional Ca and P most effectively. Standard cow milk formula and soy-based formulas (potential for low bioavailability of Ca and P due to phytate P binding) provide inadequate Ca and P for preterm infants. Table 2 lists sample mineral contents for the most commonly used sources of preterm infant nutrition.

Phosphate depletion and osteopenia occur rapidly in preterm infants fed unsupplemented human milk due to its low phosphate content. When hypophosphatemia is present, only limited amounts of Ca can be deposited in bone, resulting in hypercalcemia and hypercalciuria. If phosphate repletion occurs alone, it stimulates bone mineralization, leading to subnormal Ca levels (“hungry bones” syndrome). For the infant in the vignette, therefore, neither calcium gluconate nor potassium phosphate alone would be sufficient supplementation.

The standard infant formulations of multivitamins contain additional vitamin D as well as vitamins A, C, E, and K, depending on the preparation. Vitamin deficiency rarely is the cause of osteopenia in preterm infants. Supplementation of vitamin D up to 2,000 IU/d has not been effective in reducing the incidence of osteopenia. Multivitamins do not provide additional Ca or P.

Vitamin D is a fat-soluble vitamin available from dietary sources or via synthesis in the skin from cholesterol by a light-dependent process. Even the most immature infants can absorb and metabolize vitamin D within days after birth. 1,25-dihydroxyvitamin D is the most metabolically active of the more than 30 metabolites whose major physiologic action is to increase bone mineralization by increasing small bowel absorption of Ca and P. Together with parathyroid hormone, vitamin D maintains serum calcium homeostasis. Human milk contains very small amounts of vitamin D (<20 IU/L). Current recommendations suggest that a minimum of 160 to 400 IU/d is required for preterm infants. Higher doses of vitamin D have not been shown to increase bone mineralization, as measured by biochemical or radiographic differences. Vitamin D deficiency is rare in the very low-birthweight infant because of the use of supplemental vitamin D in parenteral nutrition and infant formulas.

The ideal duration of Ca and P mineral supplementation is not known, although current conservative recommendations suggest continuing full supplementation until term body size is attained, biochemical markers are normal, and radiographic evidence of healing is present. Continued use of a mineral-enriched diet has resulted in better growth and bone mineralization at 9 months of age. Osteopenia appears to be self-resolving disease, with radiographic resolution by 6 months of age, but the long-term consequences of a period of demineralization and its effect on the attainment of peak bone mass are not known. Peak serum alkaline phosphatase levels greater than 1,200 U/L have correlated with decreased body length at 18 months of age. Dental enamel hypoplasia when tooth eruption occurs also has been associated with osteopenia. Avoidance of fractures and decreased dolichocephaly may be benefits of prevention and treatment.

References:


**Content Specifications:**

Understand the etiology, clinical manifestations, radiographic features, and approach to treatment of osteopenia of prematurity

Understand the interrelated effects of various hormones, including parathormone, calcitonin, and Vitamin D on calcium, phosphorous, and magnesium metabolism in the fetus and neonate

Recognize the relationship between the calcium and phosphorous content of parenteral nutrition solutions and osteopenia

Understand the mineral and vitamin content of infant formulas

Be familiar with the ability of human milk, infant formulas, and milk fortifiers to meet the needs of the very low-birth-weight infant
Table 1

<table>
<thead>
<tr>
<th>Risk Factors for Osteopenia of Prematurity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity less than 34 weeks gestational age</td>
</tr>
<tr>
<td>Birth weight less than 1500 grams</td>
</tr>
<tr>
<td>Feedings of unsupplemented human milk</td>
</tr>
<tr>
<td>Medical complications</td>
</tr>
<tr>
<td>Delayed establishment of enteral nutrition</td>
</tr>
<tr>
<td>Prolonged parenteral nutrition</td>
</tr>
<tr>
<td>Cholestatic jaundice</td>
</tr>
<tr>
<td>Fluid restriction</td>
</tr>
<tr>
<td>Immobility</td>
</tr>
</tbody>
</table>

Medications

   Diuretics
   Dexamethasone
   Sodium Bicarbonate
   Theophylline
Table 2

<table>
<thead>
<tr>
<th>Formula</th>
<th>Calcium (mg/l)</th>
<th>Phosphorous (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 cal/oz premature infant formula</td>
<td>784 – 890</td>
<td>462 – 890</td>
</tr>
<tr>
<td>24 cal/oz premature infant formula</td>
<td>1340 – 1452</td>
<td>670 – 806</td>
</tr>
<tr>
<td>20 cal/oz soy based formula</td>
<td>709 – 710</td>
<td>507 – 560</td>
</tr>
<tr>
<td>20 cal/oz bovine formula</td>
<td>530 – 726</td>
<td>360 – 565</td>
</tr>
<tr>
<td>Human milk</td>
<td>270 – 320</td>
<td>130 – 150</td>
</tr>
<tr>
<td>24 cal/oz fortified human milk</td>
<td>1140 – 1380</td>
<td>590 – 776</td>
</tr>
</tbody>
</table>
A pediatrician calls for your advice regarding a 2-month-old infant who presents with a 1-week history of intermittent vomiting appears jaundiced on physical examination. At 4 weeks of age, the exclusively breastfed baby was gaining weight well and was not icteric. The mother subsequently returned to work, and the infant has been receiving supplements of formula and apple juice while at day care. A urine test for reducing substances is positive.

Of the following, the MOST likely cause of jaundice in this infant is

1. alpha-1-antrypsin deficiency
2. biliary atresia
3. cystic fibrosis
4. fructose intolerance
5. homocystinuria

You selected 2, the correct answer is 1.

A careful history and physical examination coupled with fractionation of the bilirubin can begin to narrow the etiologic possibilities and guide the evaluation of the infant who appears jaundiced. The development of jaundice and vomiting with the introduction of fruit juice in the diet of the infant in the vignette suggests the diagnosis of fructose intolerance, which is supported by a positive urine test for reducing substances. A definitive diagnosis is made by the measurement of fructose 1,6-biphosphate aldolase activity in liver tissue. Fruit juices are not recommended for 2-month-old infants.

The presence of jaundice in a 2-month-old infant may be caused by an increase in serum levels of unconjugated (indirect), conjugated (direct), or both forms of bilirubin. Physiologic hyperbilirubinemia of the newborn should resolve by 2 weeks of age, and prolonged jaundice associated with breastfeeding rarely persists beyond the first 8 postnatal weeks. Unconjugated hyperbilirubinemia may be the result of an increased bilirubin load due to hemolytic disorders, enterohepatic recirculation (eg, cystic fibrosis and pyloric stenosis), hypothyroidism, sepsis, drugs, or other underlying conditions. Direct hyperbilirubinemia may be due to infectious, toxic, metabolic, or genetic causes; functional impairment of bile secretion; or mechanical obstruction of bile excretion.

Infectious causes include viral hepatitis (eg, cytomegalovirus; hepatitis A, B, or C) toxoplasmosis, and syphilis. Toxic causes include parenteral nutrition and drugs such as erythromycin. Among the metabolic diseases are disorders of carbohydrate metabolism (eg, galactosemia, fructosemia), disorders of amino acid metabolism (eg, tyrosinemia), and disorders of lipid metabolism (eg, Niemann-Pick, Gaucher disease). Down syndrome, Turner syndrome, and other conditions, such as alpha-1-antitrypsin deficiency, hypothyroidism, and cystic fibrosis, have been associated with elevated levels of conjugated bilirubin. Intrahepatic duct disease (eg, neonatal hepatitis, Alagille syndrome) and extrahepatic duct failure (eg, biliary atresia, sclerosing cholangitis, choledochal cyst) lead to obstruction of bile flow.

Some infants who have alpha-1-antitrypsin deficiency, progressive liver disease, or cystic fibrosis may be jaundiced and have elevated conjugated bilirubin levels. However, the history and presence of reducing substances makes these less likely causes of jaundice for the infant in the vignette. Homocystinuria, a disorder of amino acid metabolism, is not associated with jaundice in early infancy. Characteristic features of this progressive disorder include Marfanlike habitus, developmental delay, downward subluxation of the ocular lens, and osteoporosis, with
the development of thromboembolism in the second decade of life.

References:

Full text available online for subscription or fee.

Full text is available online for subscription or fee.


Content Specifications:

Know the factors associated with an increase in neonatal serum bilirubin concentrations

Understand the differential diagnosis, evaluation, and approach to management of mixed forms of jaundice
A 7-day-old term African-American female infant presents with abnormal movements for the last two days. The abnormal movements consist of shaking of the head and left arm with twitching of the left eye, which then go on to involve the whole body. These episodes last a total of 10 to 35 seconds and occur four to six times a day. There is no loss of consciousness, cessation of breathing, or change in color or tone. There is no history of trauma. She is being fed regular infant formula with iron. There is no history of altered intake, elimination, temperature instability, respiratory distress or lethargy. Perinatal history is unremarkable. Physical examination reveals an awake, alert, active, afebrile infant without respiratory distress, and an unremarkable systemic examination. Complete blood count, head ultrasonography, and electroencephalography showed no abnormalities.

The laboratory data reveals:

Work-up

<table>
<thead>
<tr>
<th></th>
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<th>iPTH</th>
<th>18 pg/mL (1.9 pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>142 mEq/L (142 mmol/L)</td>
<td>iPTH</td>
<td>18 pg/mL (1.9 pmol/L)</td>
</tr>
<tr>
<td>Potassium</td>
<td>5.9 mEq/L (5.9 mmol/L)</td>
<td>1,25 (OH)2 Vitamin D</td>
<td>112 pg/mL (268.8 nmol/L)</td>
</tr>
<tr>
<td>Chloride</td>
<td>107 mEq/L (107 mmol/L)</td>
<td>Maternal s calcium</td>
<td>9.6 mg/dL (2.4 mmol/L)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>23 mEq/L (23 mmol/L)</td>
<td>Glucose</td>
<td>74 mg/dL (4.1 mmol/L)</td>
</tr>
<tr>
<td>BUN</td>
<td>5 mg/dL (1.8 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.4 mg/dL (35.4 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>6.1mg/dL (1.5 mmol./L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.8 mg/dL (0.7 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>10.5 mg/dL (3.4 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.4 g/dL (34 g/L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Of the following, the MOST likely cause of seizures in this infant is:

1. early neonatal hypocalcemia
2. late neonatal hypocalcemia
3. maternal parathyroid adenoma
4. primary hypoparathyroidism
5. vitamin D deficiency

You selected 5, the correct answer is 2.

Hypocalcemia is one of the most common causes of neonatal seizures. Hypocalcemia in term infants is defined as an ionized calcium (Ca) concentration of <4.4 mg/dL (1.10 mmol/L). If an ionized Ca measurement is not available, the traditional definition - total serum Ca <8 mg/dL (4
mmol/L) can be used. In clinical practice, the diagnosis of hypocalcemia is based on the determination of ionized or total Ca. Serum magnesium (Mg) also should be measured, because hypomagnesemia may coexist and cause identical signs. Measurement of Ca-regulating enzymes is not recommended routinely unless hypocalcemia is prolonged, refractory, or recurrent.

The clinical and laboratory findings in the vignette are most consistent with late hypocalcemia.

Late hypocalcemia in neonates, much less common than early hypocalcemia, is due to intake of milk with a high content of phosphate. The onset of symptoms occurs most commonly during the first 5 to 10 days after birth, although clinical manifestations occasionally have appeared as late as 6 weeks after birth. Late neonatal hypocalcemia frequently was observed in infants fed cow's milk because of the high phosphate (P) content (956 mg/L). With the introduction of adapted infant formulas, late hypocalcemia, although not abolished, has become uncommon. Even with current formulas, however, formula-fed infants have lower serum ionized Ca and higher P in the first week of life, compared to breastfed infants. These differences do not correlate with different Ca:P ratios in formulas but rather with their absolute P amount: breast milk has about 140 mg/L of phosphorus, and current standard formula has at least twice as much phosphorus (280 mg/L). Although the higher P content of formulas, compared with human milk, may represent a risk factor for hypocalcemia, other factors must play a role, given the clinical rarity of this condition.

Late neonatal hypocalcemia most often occurs in otherwise healthy, full-term neonates. The intake of a high-phosphorus food in a relatively large volume, combined with decreased renal phosphorus excretion, leads to elevated serum phosphorus. The decreased renal phosphorus excretion is due to the physiologically low glomerular filtration rate of the newborn and the relatively high tubular reabsorption of phosphorus. The elevated serum phosphorus depresses serum calcium through deposition of calcium phosphorus in bone and possibly in other tissues. The normal physiologic response is an increased output of parathyroid hormone (PTH), which stimulates calcium release from bone and urine phosphorus excretion. This restores the normal serum levels of calcium and phosphorus.

Infants with late neonatal hypocalcemia may have normal or elevated PTH, but the PTH response is relatively inadequate because the serum calcium is low. In affected children, the immature parathyroid gland may not be able to respond appropriately. Alternatively, some of these infants may have an appropriate PTH response to hypocalcemia, but have end-organ resistance to PTH. This "transient pseudohypoparathyroidism" resolves itself.

Early neonatal hypocalcemia occurs during the first 72 hours after birth, usually before the infant achieves a significant oral intake of milk. Serum calcium reaches a nadir at approximately 24 hours. There are many mechanisms that account for early neonatal hypocalcemia. At birth, there is an interruption of the transplacental delivery of calcium, an active process that maintains a higher calcium level in the fetus than in the mother. In addition, newborns may have a relative hypoparathyroidism, attributed to the increased serum calcium of the fetus, which causes suppression of the parathyroid gland. Newborns also may have a relative refractoriness of the target cells to PTH. Other predisposing factors for early neonatal hypocalcemia are prematurity, maternal diabetes, perinatal asphyxia, and maternal anticonvulsants.

Hypocalcemia may occur in infants of mothers with hypercalcemia, which is commonly due to hyperparathyroidism from a parathyroid adenoma. The constant in utero suppression of the parathyroid gland can lead to neonatal hypoparathyroidism that is prolonged, sometimes lasting for months. The infants usually develop tetany during the first three weeks after birth, but it may occur later if the infant is breastfed. Often, the mother is asymptomatic, and the diagnosis depends on the length of time before maternal serum calcium is determined. Normal maternal calcium, as seen in this vignette, rules out maternal hyperparathyroidism.

There are many causes of primary hypoparathyroidism, including X-linked, autosomal recessive or dominant trait, association with ring chromosomes, or as part of the DiGeorge syndrome. In these conditions, along with hypocalcemia, hypoparathyroidism leads to hyperphosphatemia due to decreased renal excretion of phosphorus. PTH levels are either low or undetectable, although inappropriately normal levels in the setting of hypocalcemia may occur in children with some residual PTH production. Because PTH and hypophosphatemia are the normal stimuli for
the renal 1α-hydroxylase, 1,25-dihydroxyvitamin D levels are low. Normal 1,25-dihydroxyvitamin D and PTH levels in this vignette rule out primary hypoparathyroidism.

In vitamin D deficiency, hypocalcemia is primarily the result of poor intestinal calcium absorption. PTH levels increase as a response to the inadequate calcium, and this initially prevents the development of frank hypocalcemia by causing release of calcium from bone, decreasing urinary losses of calcium, and upregulating the activity of the 1α-hydroxylase that converts 25-hydroxyvitamin D into the active form of vitamin D, 1,25-dihydroxyvitamin D. When these compensatory mechanisms are inadequate, hypocalcemia develops. Most children with inadequate vitamin D receive medical attention for rickets before developing hypocalcemia. Children with vitamin D deficiency have elevated serum PTH, and, because of increased osteoclast activity, elevated serum alkaline phosphatase. Serum phosphorus is usually low due to decreased intestinal absorption and increased urinary excretion secondary to the effect of PTH. Vitamin D deficiency may be secondary to poor intake combined with inadequate exposure to ultraviolet light from the sun. In the United States, this condition is most common in African-American children who are breastfed but do not receive vitamin D supplementation.

References:


Content Specifications:

Understand the etiology and clinical manifestations of neonatal hypocalcemia

Understand the laboratory features and approach to therapy of neonatal hypocalcemia
A woman is screened for glucose intolerance during pregnancy at 30-weeks’ gestation. Her blood glucose measures 144 mg/dL (8 mmol/L) one hour after a 50-g oral glucose challenge. After an overnight fast, her blood glucose is 108 mg/dL (6 mmol/L). Two hours after a 75-g oral glucose load, it is 180 mg/dL (10 mmol/L). These results are consistent with glucose intolerance of pregnancy. Her physician recommends dietary advice, blood glucose monitoring, and potential insulin treatment.

Of the following, the neonatal outcome MOST improved by screening for and treating gestational diabetes is:

1. admission for neonatal intensive care
2. hypoglycemia requiring intravenous glucose
3. jaundice requiring phototherapy
4. macrosomia
5. respiratory distress needing oxygen for >4 hours

You selected 5, the correct answer is 1.

Gestational diabetes (carbohydrate intolerance) first recognized during pregnancy affects 1.4% to 14% of pregnancies. Glucose regulation during pregnancy becomes more challenging to the mother as pregnancy progresses. Because the fetus continuously and increasingly draws glucose across the placenta, interprandial hypoglycemia becomes more pronounced in later pregnancy.

Maternal blood glucose decreases to 55 to 65 mg/dL (3.1 to 3.6 mmol/L) after overnight fasting. Concentrations of estrogens, progesterone, and chorionic somatomammotropin (all diabetogenic hormones) rise linearly in the second and third trimesters, resulting in maternal tissue resistance to insulin, which requires a doubling of pancreatic insulin output to maintain euglycemia. If maternal insulin production is inadequate, maternal (and then fetal) hyperglycemia occurs.

Fetal hyperinsulinemia results in excessive storage of nutrients and fetal macrosomia. Insulin also stimulates catabolism of excess glucose, consuming oxygen stores. Hypoxia then can result in release of adrenal catecholamines, which can precipitate a cascade of hypertension, cardiac hypertrophy, erythropoietin release, and elevated hematocrit.

Perinatal complications associated with gestational diabetes include macrosomia, shoulder dystocia, birth injuries (especially nerve palsies and fractures), cesarean delivery, and hypoglycemia of the newborn. Perinatal mortality is not affected by gestational diabetes. Gestational diabetes is a risk factor for subsequent diabetes mellitus in the mother, and infants may have impaired glucose tolerance, obesity, and impaired intellect.

Screening for gestational diabetes remains controversial. The U.S. Preventative Services Task Force finds insufficient evidence to recommend either in favor of or against routine screening. In contrast, the American College of Obstetricians and Gynecologists recommends screening and treatment, albeit based on "limited or inconsistent scientific evidence." The American Diabetes Association recommends that screening be limited to women with risk factors, suggesting that screening women older than age 25 years with normal weight, no history of abnormal glucose tolerance, no family history of diabetes among first-degree relatives, no history of poor obstetric outcome, and no ethnic or racial basis for risk is not cost-effective.
spite of these diverse recommendations, universal screening is included in the prenatal care of many pregnant women.

In a recent randomized controlled study (Crowther and associates) of gestational diabetes morbidities, screening for and treatment of the mother's condition affected fetal size, with reductions noted in incidence of large-for-gestational-age infants, ie, infants >90th percentile for gestational age (Relative risk [RR] 0.62; 95% confidence interval [CI] 0.47 to 0.81) and in incidence of macrosomia, ie, >4 kg birthweight (RR 0.47; 95% CI 0.34 to 0.64). Treatment of gestational diabetes showed no effect on perinatal mortality. When compared to infants of mothers with similar blood-sugar concentrations who received normal obstetrical care, infants born to mothers screened and treated for gestational diabetes showed a reduced risk for the combination of mortality with the morbidities of shoulder dystocia, bone fracture, and/or nerve palsy (RR 0.32; 95% CI 0.14 to 0.75). Mothers in the screened group were more likely to undergo induction of labor, but no more likely to be delivered by cesarean section. This study and the accompanying editorial (Greene and Solomon) support the evaluation for and treatment of gestational diabetes.

Many questions still remain, however, regarding precise diagnostic criteria and the exact relationship between gestational diabetes and perinatal outcomes. Among infants delivered to mothers screened and treated for gestational diabetes, admission for neonatal intensive care increased rather than decreased. Infants of the treated mothers showed no reductions in hypoglycemia requiring intravenous glucose, jaundice requiring phototherapy, or respiratory distress requiring oxygen beyond four hours after birth compared to infants of mothers whose glucose screening concentrations were similar but who were given standard obstetric care.

References:


Content Specifications:

Know the rationale and methods for screening for glucose intolerance in pregnancy

Understand the implications of fetal macrosomia
A term male infant develops temperature instability, hypothermia, and hypoglycemia. On physical examination, he has pudgy cheeks and sagging jowls. His hair and eyebrows are sparse, brittle, and silver-colored. Microscopic examination of the hair shows pili torti. Family history is significant for a brother who had similar hair and eyebrows. The brother developed seizures at age 3 months and died at age 2 years after progressive neurologic deterioration.

Of the following, the trace element whose dysfunctional metabolism is MOST likely to account for the genetic disorder in this family is:

- [ ] chromium
- [ ] copper
- [ ] manganese
- [x] selenium
- [ ] zinc

You selected selenium, the correct answer is copper.

An element is considered a trace element if it constitutes <0.01% of total body weight. Trace elements include chromium (Cr), cobalt, copper (Cu), fluoride, iodine, iron, manganese (Mn), molybdenum, nickel, selenium (Se), silicon, vanadium, and zinc (Zn). Trace elements play important roles in metabolism as essential components of metalloenzymes or as cofactors for enzymes. Trace element homeostasis is a tightly regulated process. Dietary deficiencies in trace elements are most severe during periods of rapid growth. Excess intake of trace elements can result in toxic accumulations. There are several rare genetic disorders that result in life-threatening accumulations or deficiencies of trace elements.

The family described in this vignette has Menkes disease (MD), also known as kinky hair disease. MD is a lethal, X-linked, recessive disorder of Cu metabolism. The incidence of MD in the United States is 1 in 300,000 live births. Internationally, MD is most common in Australia, where the incidence is 1 in 35,000 live births.

The clinical features of MD include silvery, sparse, brittle, steel-wool-like hair. Hair changes may not be present in the newborn period. Skin is hypopigmented, mottled, doughy, and lax. Seizures begin within the first few days or months after birth. Progressive neurologic deterioration occurs, marked by loss of developmental milestones, hypotonia, hypothermia, and lethargy. Most patients die by age 3 years. MD is characterized by a systemic Cu deficiency due to a defect in intestinal Cu transport. Cu is essential for brain metabolism, serving as a cofactor to amyloid precursor protein, dopamine-beta-hydroxylase, superoxide dismutase, and ceruloplasmin. Impaired Cu metabolism during early development leads to severe neurodegeneration. Parenteral administration of Cu can modify the course of the disease if started shortly after birth.

Cr serves as a cofactor for insulin. The biologically relevant form of Cr is the trivalent ion. Cr3+ is required for proper carbohydrate and lipid metabolism. There are no known genetic disorders of Cr3+ metabolism. Cr3+ deficiency may occur during prolonged parenteral nutrition or may be associated with protein calorie malnutrition. Cr3+ deficiency may result in impaired glucose metabolism.

Mn is a cofactor for enzymes such as Mn superoxide dismutase, arginase, pyruvate carboxylase, and glutamate-ammonia ligase. There are no known genetic disorders of Mn
metabolism. Although there are no documented abnormalities in humans deficient in Mn, animals deficient in Mn exhibit growth restriction, ataxia, and bone abnormalities. Of greater concern than Mn deficiency is Mn toxicity. Mn excess has been reported through dietary and occupational (as in welders) exposure. Mn toxicity causes confusion, muscle cramps, and poor coordination. Accumulation of Mn in brain tissue can result in a progressive disorder of the extrapyramidal system similar to Parkinson disease. Excessive Mn in children receiving long-term parenteral nutrition may contribute to cholestatic disease.

Se is an essential component of several proteins, including Se-dependent glutathione peroxidase, selenoprotein P, and deiodinase. Se is incorporated into these proteins as selenocysteine. Glutathione peroxidase is important in protecting lipids in polyunsaturated membranes from oxidative degradation. Impaired glutathione peroxidase antioxidant activity is important in oxidative diseases, such as bronchopulmonary dysplasia and retinopathy of prematurity. There are no known genetic disorders of Se metabolism. Inadequate concentrations of Se in the Chinese diet account for the development of Keshan disease, a form of juvenile cardiomyopathy that has a dual cause of Se deficiency and enteroviral infection. Toxicity from Se excess is minor. Excessive Se intake causes irritation of mucous membranes, irritability, pallor, and indigestion.

Zn is an integral cofactor for many enzymes involved in nucleic acid and protein metabolism. Zn is an important component of DNA and RNA polymerase, transcription factors (Zn-fingers), and enzymes involved in energy metabolism. Acrodermatitis enteropathica (AE) is an autosomal recessive disorder of Zn metabolism. AE is caused by the reduced uptake of dietary Zn by enterocytes, and the ensuing systemic Zn deficiency. Clinical features of AE are similar to those of severe dietary Zn deficiency and include alopecia, perioral and acral bullous lesions, diarrhea, and impaired growth. Symptoms usually begin two to three weeks after weaning from breast milk, because breast milk contains a Zn binding factor that augments Zn absorption. Formula-fed infants with AE become symptomatic one to two months after birth. The gene responsible for AE encodes a protein involved in dietary Zn uptake from the intestinal lumen. Supplemental oral Zn can overcome the deficiency in intestinal Zn absorption and improve the clinical features of AE.

References:


Vincent JB. Recent advances in the nutritional biochemistry of trivalent chromium. Proc Nutr Soc. 2004;63:41-47

Content Specifications:

Understand the clinical manifestations and diagnosis of zinc deficiency

Understand the management and prevention of zinc deficiency

Understand the clinical manifestations and diagnosis of copper deficiency

Understand the management and prevention of copper deficiency

Understand the clinical manifestations and diagnosis of selenium deficiency
Understand the management and prevention of selenium deficiency
Understand the clinical manifestations and diagnosis of manganese deficiency
Understand the management and prevention of manganese deficiency
Understand the clinical manifestations and diagnosis of chromium deficiency
Understand the management and prevention of chromium deficiency
A 36-hour-old male newborn, whose estimated gestational age at birth is 38 weeks and whose growth measurements are: birthweight 1,800 g (<5th percentile for gestational age), crown-heel length 46 cm (10th percentile), and head circumference 34 cm (50th percentile), has blood glucose of 24 mg/dL (1.3 mmol/L). The infant is receiving a continuous infusion of 15% glucose through an umbilical venous catheter at a rate of 9 mL per hour and no enteral feeds. He has no clinical evidence of respiratory distress, cardiac dysfunction, thermal imbalance, central nervous system manifestations, or sepsis.

Of the following, the MOST likely cause of hypoglycemia in this infant is:

1. excessive utilization of glucose
2. hyperinsulinism
3. impaired gluconeogenesis
4. inadequate intake of glucose
5. insensitivity to glucagon

You selected 2, the correct answer is 3.

The infant in this vignette is small for gestational age (SGA) whose cranial growth is relatively spared, consistent with asymmetric intraterine growth restriction. Hypoglycemia, defined as blood glucose less than 30 mg/dL (1.7 mmol/L) is common in SGA infants. Hypoglycemia represents an imbalance between glucose influx into circulation and glucose efflux from circulation. The glucose influx into circulation is determined largely by exogenous intake of glucose, endogenous release of glucose from glycogen principally in the liver (glycogenolysis), and endogenous synthesis of glucose from nonglucose precursors (gluconeogenesis). The glucose efflux from circulation is determined largely by glucose utilization in the peripheral tissues, principally mediated by insulin.

Among the options in the vignette, the most common cause of hypoglycemia in SGA infants is impaired gluconeogenesis. Inadequate stores of glycogen also contribute to hypoglycemia. The gluconeogenesis pathway involves both mitochondrial and cytosolic enzymes (Figure 1). The formation of glucose or glycogen from pyruvate involves entry of pyruvate into the mitochondria and its conversion by pyruvate carboxylase (PC) to oxaloacetate. The oxaloacetate is converted to malate directly as well as indirectly through alpha-ketoglutaric acid, a product of deamination of glutamine. The malate exits the mitochondria and is reconverted to oxaloacetate in the cytosolic compartment. The oxaloacetate is converted to phosphoenolpyruvate by phosphoenolpyruvate carboxykinase (PEPCK). The phosphoenolpyruvate then is converted via a number of reversible steps into fructose 1,6-bisphosphate, which is a precursor for fructose-6-phosphate, a reaction catalyzed by fructose 1,6-bisphosphatase (F1,6-Bpase). Glucose-6-phosphate, derived from fructose-6-phosphate, is the immediate precursor for glucose, a reaction mediated by glucose-6-phosphatase (G6-Pase), and is the common intermediate for both glycogenolysis and gluconeogenesis. In addition to glutamine, the other key gluconeogenic precursors include alanine, lactate, and glycerol. Impaired gluconeogenesis as a consequence of lower activity of the key gluconeogenesis enzymes - PC; PEPCK; F1, 6-; and G6-Pase - offers the best explanation for hypoglycemia in SGA infants.

Hypoglycemia from excessive utilization of glucose in the peripheral tissues may occur with the increased work of breathing associated with respiratory disease, a shift in energy metabolism from aerobic to anaerobic pathways associated with circulatory disease, increased caloric...
expenditure for thermoregulation, and increased glucose consumption by the brain. The latter may be associated with seizures, intoxication, meningitis, encephalitis, hypoxic-ischemic injury, trauma, and intracranial hemorrhage. The absence of such abnormalities in the infant in this vignette makes it unlikely that excessive utilization of glucose was the principal contributor to hypoglycemia.

Hypoglycemia secondary to hyperinsulinism is seen typically in the infant of a diabetic mother, the neonate with hemolytic disease, and the neonate with nesidioblastosis or islet cell adenomatosis. Other common causes of hyperinsulinemic hypoglycemia include genetic syndromes such as Beckwith-Wiedemann syndrome, maternal conditions such as beta-sympathomimetic treatment and ethanol consumption, and neonatal interventions, including placement of a high umbilical arterial catheter and exchange transfusion. Although hyperinsulinism can occur in sporadic cases, the pattern of secretion of insulin in SGA infants is usually similar to that seen in infants appropriately grown for their gestational age.

A full-term healthy human newborn subjected to fasting for 3 to 4 hours after birth produces glucose at a rate of 4 to 6 mg/kg per minute. This endogenous glucose production is sustained by the contributions of both glycogenolysis and gluconeogenesis. The oxygen consumption rate of the brain in such a newborn has been determined to be approximately 104 umol/100g brain tissue per minute. If the average weight of the brain is estimated to be 360 g, approximately 3.7 mg/kg per minute of glucose production would be required to meet the metabolic needs of the brain. In contrast, in SGA infants the glycogen stores may be depleted and gluconeogenesis is impaired. The brain size in relation to body size is greater, thereby increasing the oxygen demand. Thus, in the absence of an adequate exogenous intake, the endogenous production of glucose may not be sufficient to avert hypoglycemia. An intake of glucose to sustain a glucose infusion rate of 6 to 8 mg/kg per minute may be warranted.

Although the infant in this vignette is not receiving enteral feeds, he is receiving a constant glucose infusion through the umbilical venous catheter at a rate that can be calculated to be 12.5 mg/kg per minute. Persistence of hypoglycemia despite this high glucose intake warrants further diagnostic evaluation and other therapeutic options.

Glucagon is a peptide hormone released by the alpha cells of the pancreatic islets. Its major target tissue is the liver, and its principal action is stimulation of glycogenolysis with resultant release of glucose into circulation. Glucagon acts in concert with insulin to maintain euglycemia. Studies of glucagon in SGA infants have revealed no abnormalities of glucagon structure, secretion, or function. The lack of effect of glucagon in raising blood glucose in SGA infants may be explained by the lack of glycogen stores in the liver.

References:


Content Specifications:

Know the amino acid substrates for gluconeogenesis

Know the normal range of endogenous glucose production in term and preterm infants
Recognize the etiology and clinical manifestations of neonatal hypoglycemia
Recognize the laboratory features of neonatal hypoglycemia
A 14-day-old male newborn, who weighs 1000 g at an estimated postmenstrual age of 28 weeks, has a blood glucose concentration of 185 mg/dL (10.3 mmol/L). The infant is receiving no enteral feeds because of feeding intolerance, but he is receiving parenteral nutrition through a percutaneous central venous catheter that contains 12.5 g/dL of glucose and 3 g/dL of protein infusing at a rate of 4.8 mL/hr, and 3 g/dL of lipid infusing at a rate of 0.5 mL/hr. He is receiving mechanical ventilation for recurrent apnea and antimicrobial therapy pending blood culture results. Previous blood glucose concentrations on this regimen have been in the normal range.

Of the following, the PRIMARY cause of hyperglycemia in this infant is abnormal secretion of:

- catecholamines
- glucagon
- growth hormone
- insulin
- somatostatin

You selected 2, the correct answer is 1.

The extremely low birthweight (ELBW) neonate in this vignette has hyperglycemia of acute onset. Hyperglycemia is defined as a blood glucose concentration in excess of 150 mg/dL (8.3 mmol/L). This concentration falls outside the upper limit of the normal range of blood glucose concentrations in ELBW neonates, providing the basis for the statistical definition of hyperglycemia. At this concentration, the counterregulatory hormones of glucose homeostasis are likely to be triggered, providing the basis for the physiologic definition of hyperglycemia. In addition, at this concentration, clinical adverse effects, including glycosuria, are likely, providing the basis for the pathologic definition of hyperglycemia. The development of sudden hyperglycemia in a previously euglycemic ELBW neonate, as in the infant in this vignette, raises the possibility of acute stress as the cause of hyperglycemia. The symptoms of feeding intolerance and recurrent apnea warranting ventilatory assistance raise the suspicion of sepsis as the cause of acute stress in this infant.

Hyperglycemia represents an imbalance between glucose influx into circulation and glucose efflux from circulation. The glucose influx into circulation is determined largely by exogenous intake of glucose, endogenous release of glucose from glycogen principally in the liver (glycogenolysis), and endogenous synthesis...
of glucose from nonglucose precursors (gluconeogenesis). The glucose efflux from circulation is determined largely by glucose utilization in peripheral tissues, principally mediated by insulin. The infant in this vignette is receiving glucose infusion at a rate that can be calculated to be 10 mg/kg per min. This rate makes it unlikely that excessive exogenous intake of glucose is the cause of hyperglycemia (iatrogenic hyperglycemia) in this infant. Rather, it raises the possibility of hormonal imbalance as its cause.

The mechanism of stress-induced hyperglycemia primarily involves the secretion of catecholamines and/or cortisol. Catecholamines (dopamine, norepinephrine, and epinephrine) are the products of the sympathoadrenal medullary system and are the principal mediators of responses to both acute and chronic stress. Catecholamines increase glucose production directly by stimulating both glycogenolysis and gluconeogenesis, and indirectly by stimulating glucagon release. Epinephrine also decreases glucose utilization directly by inhibiting tissue glucose uptake and indirectly by suppressing insulin release. Among the catecholamines, epinephrine is the most potent in inducing stress-related hyperglycemia.

Glucagon is a peptide hormone derived from alpha cells of the pancreatic islets. Its major target tissue is the liver, and its principal action is stimulation of glycogenolysis, with release of glucose into circulation. In addition, glucagon stimulates hepatic gluconeogenesis and ketogenesis. Because glucagon acts in concert with insulin to maintain euglycemia, the hyperglycemic effect of glucagon is largely evident as a compensatory response to insulin-induced hypoglycemia. Also, the hyperglycemic effect of glucagon rarely is sustained, as it is countered by stimulation of glucagon-induced insulin release. Moreover, the hyperglycemic effect of glucagon may fail to occur when the hepatic glycogen stores are limited, as in some ELBW neonates. Thus, glucagon is not the primary mediator of stress-related hyperglycemia.

Growth hormone is a peptide hormone secreted by somatotrophs of the anterior pituitary. As a counterregulatory hormone in defense against hypoglycemia, growth hormone exerts its metabolic effects in a biphasic manner. During the early phase, growth hormone exerts insulin-like effects characterized by suppression of hepatic glucose output and stimulation of tissue glucose clearance. During the latter phase, growth hormone exerts anti-insulin effects characterized by increased hepatic glucose production and decreased tissue glucose uptake. The hyperglycemic effect of growth hormone is largely evident as a compensatory response to hypoglycemia, is delayed in its occurrence, and rarely is sustained. Thus, growth hormone is not the primary mediator of stress-related hyperglycemia.

Insulin is a peptide hormone secreted by beta cells of the pancreatic islets. It is the major regulator of glucose homeostasis and related metabolic events. Diabetes mellitus is classified broadly into two categories: insulin-dependent (type I) diabetes mellitus, characterized by impaired secretion of insulin; and noninsulin-dependent (type II) diabetes mellitus, characterized by peripheral tissue resistance to insulin. Neonatal diabetes mellitus from insulin deficiency or resistance is rare (1 in 500,000 live births). It occurs mostly in small-for-gestational-age infants, manifests typically during the first 6 weeks after birth, and often is sporadic, although familial cases with or without dysmorphic features, such as macroglossia, hypertelorism, and club feet, have been reported. The infants present with failure to thrive, dehydration, severe hyperglycemia with blood glucose concentrations often exceeding 200 to 300 mg/dL (11.1 to 16.7 mmol/L), glycosuria with or without ketonemia and ketonuria, and metabolic acidosis. In approximately 31% of cases, the diabetes is transient and resolves completely in the neonatal period; in 23% of cases, the diabetes resolves initially, only to recur during childhood and adolescence; and in 46% of cases, the diabetes is permanent. The latter is more likely in familial cases, especially in infants with human leukocyte antigen (HLA)-DR3 and HLA-DR4 haplotypes. The absence of
such clinical and biochemical features makes neonatal diabetes mellitus an extremely unlikely cause of hyperglycemia in the infant in this vignette.

Somatostatin is a peptide hormone synthesized in neurons in the anterior periventricular region of the hypothalamus. It is distributed widely throughout the body, including in many central nervous system regions and the digestive tract tissues. In the pancreas, it is contained largely in the delta cells of the islets. Under normal conditions, somatostatin suppresses the release of many pituitary, pancreatic, and gastrointestinal hormones. It inhibits growth hormone and glucagon, lowering the blood glucose concentration. Thus, somatostatin is not the primary mediator of stress-related hyperglycemia.

References:


Content Specification(s):

Know the etiology and clinical manifestations of neonatal hyperglycemia, including transient diabetes mellitus.
You are asked to see an infant born at term to a 35-year-old mother with a history of phenylketonuria (PKU). The mother had been maintained on a phenylalanine-restricted diet as a child, keeping her phenylalanine concentrations consistently under 6 mg/dL (360 μmol/L), but, as an adult, she had liberalized her dietary intake without monitoring phenylalanine concentrations. Pregnancy was diagnosed at an estimated 8 to 9 weeks’ gestation by home pregnancy test, at which time a phenylalanine-restricted diet was resumed. Phenylalanine concentrations measured at the time of pregnancy diagnosis and 2 weeks later were 24 mg/dL (1440 μmol/L) and 5.5 mg/dL (330 μmol/L), respectively. Genetic testing on chorionic villus sampling revealed a 46, XY karyotype with a deletion similar to the mother’s at 12q24.1 on one allele of the 12th chromosome. Paternal chromosomes are normal, and the father does not have clinical PKU.

Of the following, the outcome for the child MOST consistent with this history is:

1. birthweight similar to general population
2. mental retardation
3. normal, because the child does not have phenylketonuria
4. significant risk for congenital heart disease
5. similar to offspring of prenatally diet-regulated maternal PKU

You selected #3, the correct answer is #4.

Phenylalanine embryopathy may result from pregnancy in mothers who have phenylketonuria (PKU). Because early diagnosis and successful dietary management have allowed many individuals affected with PKU to reach adulthood without significant impairments, infants of mothers with PKU now are being born. PKU results from an inborn error limiting the metabolism of phenylalanine to tyrosine. Inherited as an autosomal recessive condition, PKU is associated with more than 100 known mutations affecting the gene, located on the long arm of the 12th chromosome, that codes for the enzyme phenylalanine hydroxylase. Untreated patients experience progressively worsening mental retardation, which stabilizes in approximately equal proportions as either profound or moderate after completion of brain maturation. Motor abnormalities involve gait, sitting posture, and stance. Treatment consists of regulation of phenylalanine intake to maintain blood phenylalanine concentrations of 2 mg/dL to 6 mg/dL (120 μmol/L to 360 μmol/L) to age 12, the time of complete myelination of the nervous system. Tyrosine supplementation is needed for some patients. Current recommendations suggest continuing treatment throughout adulthood. Patients maintaining treatment into adulthood show reduced incidences of eczema, asthma, headache, mental disorders, hypoactivity, and hyperactivity, compared to those who do not continue dietary regulation. Diet-controlled patients also demonstrate better intellectual and achievement test results, better attention, better processing speed, and fewer abnormalities on magnetic resonance imaging.

Teratogenic risk is due to the degree and duration of elevated phenylalanine concentrations during pregnancy. Because the fetal-maternal concentration ratio is 1.35 ± 0.42 for phenylalanine, fetal teratogenicity may result from maternal concentrations that could be tolerated in the nonpregnant state. Phenylalanine embryopathy includes intrauterine growth restriction, mental retardation, microcephaly, and cardiac malformations. Among infants born to mothers with untreated PKU whose blood phenylalanine concentrations exceeded 20 mg/dL (1200 μmol/L), 73% to 92% evidenced microcephaly and mental retardation, and 12% had congenital heart disease. To best protect the fetus, maternal phenylalanine concentrations should be controlled to less than 6 mg/dL (less than 360 μmol/L) in the preconceptional period. In addition, the timing of achievement of dietary control will affect fetal risk (Table):

<table>
<thead>
<tr>
<th>Maternal PKU treatment status</th>
<th>Microcephaly (%)</th>
<th>Mean Birthweight (g)</th>
<th>Congenital Heart Disease (%)</th>
<th>Developmental Quotient (4 years)</th>
<th>Developmental Quotient (8 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>73% to 92%</td>
<td>2818</td>
<td>12% to 17%</td>
<td>[73% to 92% mental retardation]</td>
<td></td>
</tr>
<tr>
<td>By 10 weeks’ gestation</td>
<td>5%</td>
<td>2818</td>
<td>14%</td>
<td>96.8</td>
<td>86.5</td>
</tr>
</tbody>
</table>

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Preconceptional)

| Preconceptional | 3.6% | 3160 g | 1% | 108.9 | 103.4 |

Adapted from Bodhamer

In the mother in the vignette, treatment was not initiated until after 8 weeks' gestation, and desirable phenylalanine concentrations were not achieved until after the period of cardiogenesis (4 to 10 weeks' gestation). Therefore, despite maternal treatment, the infant faces a significantly higher risk for congenital heart disease. In such cases, incidences of coarctation of the aorta and hypoplastic left heart syndrome also are higher.

While dietary management of maternal PKU can limit severe intrauterine growth restriction, the onset and duration of maternal dietary management can further affect the infant's ultimate birthweight. Preconceptional onset of treatment is associated with higher mean birthweight than dietary management begun in the first 10 weeks of gestation (Table). For infants born in the situation portrayed in the vignette, mean birthweight will fall below the population mean.

Mental retardation is an unlikely outcome for the infant in the vignette, although developmental outcomes could have been improved with preconceptional onset of dietary control (Table).

The fetal embryopathy associated with maternal PKU is mediated by maternal phenylalanine concentrations and is not affected if the child does not have PKU. Therefore, the genetic testing in this vignette would not affect the infant’s susceptibility to the teratogenic effects of phenylalanine.

Preconceptional counseling is important for women with PKU who are planning to become pregnant, since preconceptional treatment affords a better prognosis than dietary management initiated early in pregnancy. According to the National Institutes of Health Consensus Development Conference on PKU, nonpregnant adults should aim for phenylalanine concentrations between 2 mg/dL and 15 mg/dL (120 μmol/L and 900 μmol/L). Moreover, recent data suggest that keeping the upper concentration under 10 mg/dL (600 μmol/L) may improve function among adults. Women with PKU should keep phenylalanine concentrations lower than 6 mg/dL (lower than 360 μmol/L) for the three months before pregnancy and during pregnancy.

References:


Sackey JA. Preconceptual evaluation and counseling. UpToDate Web site. Available at: http://www.uptodate.com

Content Specification(s):

Understand the effects on the fetus of maternal metabolic disorders (other than diabetes mellitus) and their management.
A term infant is born after a pregnancy complicated by advanced maternal age. Examination of the external genitalia reveals apparent clitoromegaly and posterior labial fusion, with palpable masses in the labial folds (Figure).

A prenatal amniocentesis had revealed a normal fetal karyotype of 46,XY. Pelvic ultrasonography suggests the presence of descended bilateral testes and intact bilateral male tubular elements (epididymis, vas deferens, and seminal vesicles). No uterus or fallopian tubes are demonstrated.

Of the following, the MOST likely diagnosis for this infant with ambiguous genitalia is:

1. deficiency in müllerian inhibiting substance
2. 5 alpha-reductase deficiency
3. placental aromatase deficiency
4. testicular feminization syndrome
5. Yp deletion with loss of the SRY gene

You selected 5, the correct answer is 2.

Normal sexual differentiation is a complex process involving chromosomal makeup, with appropriate hormonal production and effect. In both male and
female embryos, the internal genital tracts are similar and bipotential gonadal tissue develops before the seventh week of gestation. In the presence of the sex-determining region on the Y (SRY) gene, located on the short arm of the Y chromosome, the undifferentiated gonad becomes a testis, leading to a cascade of hormonal influences and male development of the fetus. In the absence of the SRY gene, the gonads become ovaries and female development occurs. Genital ambiguity and intersex conditions arise from abnormalities along the male pathway interfering with masculinization, or causing virilization of a genetic female.

In the genetic male, human chorionic gonadotropin and luteinizing hormone stimulate the Leydig cells of the testes to produce testosterone, which acts locally to stimulate the ipsilateral development of wolffian or mesonephric structures (epididymis, vas deferens, and seminal vesicles). The Sertoli cells of the testes produce müllerian inhibiting substance (MIS), which suppresses the development of the müllerian or paramesonephric structures (fallopian tubes, uterus, and upper vagina). Systemically, testosterone produced by the testes is converted by the enzyme 5α-reductase to the stronger androgen dihydrotestosterone (DHT), which causes masculinization of the external genital structures. Male differentiation is complete by 14 weeks' gestation, with subsequent penile growth and testicular descent into the scrotum by the eighth or ninth month. Incomplete or absent midline fusion of the scrotum indicates incomplete or absent androgen exposure at 8 to 14 weeks' gestation.

In the genetic female, it is largely the absence of testes rather than the presence of ovaries that influences the development of internal and external structures. The absence of MIS results in müllerian duct differentiation, and a lack of local testosterone allows degeneration of the wolffian ducts. External genital structures develop as female in the absence of sufficient effect of DHT. Labiosacral folds remain unfused to form the labia majora. External virilization in a genetic female, such as clitoromegaly, results from abnormal exposure to androgens.

The infant in the vignette presents with ambiguous external genitalia. The normal male karyotype and the presence of testes rules out an absence of the SRY gene. The absence of müllerian structures, such as the uterus, suggests adequate production of MIS from testicular Sertoli cells. Leydig cell testosterone production is supported by the presence of male tubular structures.

Testicular feminization (androgen insensitivity syndrome [AIS]), results from peripheral androgen receptor or postreceptor defects, resulting in a lack of androgenic stimulation. With complete AIS, wolffian ducts fail to develop and external genitalia are female-appearing, in contrast to the infant in the vignette. In addition, müllerian structures are absent because of sufficient testicular production of MIS. Partial AIS or incomplete testicular feminization results in incomplete masculinization of the external genitalia as well as impaired wolffian duct development.

The infant in the vignette has undervirilization of his external genitalia, with appropriate internal structures compatible with 5α-reductase deficiency. With this disorder, testosterone is produced at normal levels by the testes, acts locally to develop wolffian structures, but is not converted in peripheral tissues to DHT. Testosterone is a weaker androgen than DHT and serves as a prohormone, with DHT binding to systemic androgen receptors and inducing masculinization of external genitalia. With 5α-reductase deficiency, infants typically have apparent clitoromegaly, a urogenital sinus, and posterior labial fusion. Some patients will have hypospadias or a micropenis. The inheritance of 5α-reductase deficiency is autosomal recessive and affected females have normal genital development.

In placental aromatase deficiency, the female fetus and the mother are virilized
because of diminished placental conversion (aromatization) of fetal androgens to estrogens, and a resultant increase in circulating androgens.

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**References:**


**American Board of Pediatrics Content Specification(s):**

Understand normal fetal sexual differentiation

Differentiate among disorders of testicular hormone synthesis or action

Understand the etiology of abnormal sexual differentiation
A male newborn, whose estimated gestational age at birth is 38 weeks and whose growth measurements are: birthweight 1,800 g, crown-heel length 44 cm, and head circumference 31 cm (all less than 5th percentile for gestational age), has recurrent blood glucose less than 30 mg/dL (1.7 mmol/L). The maternal history is significant for heavy smoking throughout pregnancy.

The infant is receiving a continuous orogastric infusion of an infant formula with a carbohydrate content of 7 g/dL at a rate of 3 mL/hour, and a continuous infusion of 20% glucose through a central venous catheter at a rate of 9 mL/hour. Clinical examination reveals no evidence of respiratory distress, cardiac dysfunction, thermal imbalance, central nervous system abnormalities, hepatomegaly, or sepsis.

Laboratory data, obtained when the blood glucose was 24 mg/dL (1.3 mmol/L), reveal:

- plasma insulin 0.9 μU/mL (6.5 pmol/L) [reference range: 2 to 20 μU/mL (14.4 to 144 pmol/L)]
- plasma cortisol 5 μg/dL (138 nmol/L) [reference range: 5 to 25 μg/dL (138 to 690 nmol/L)]
- plasma growth hormone 20.2 ng/mL (20.2 g/L) [reference range: 15 to 40 ng/mL (15 to 40 μg/L)]

A decision is made to treat this infant medically while continuing the current regimen of glucose infusion.

Of the following, the drug MOST likely to be effective in correcting hypoglycemia in this infant is:

- diazoxide
- epinephrine
- glucagon
- hydrocortisone
- octreotide

You selected 2, the correct answer is 1.

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The infant in this vignette is small for gestational age (SGA), with measurements consistent with symmetric intrauterine growth restriction. Chronic placental
insufficiency from maternal smoking might have contributed to this growth pattern.

Hypoglycemia, defined as blood glucose less than 30 mg/dL (1.7 mmol/L) is common in SGA infants. The hypoglycemia in the infant in this vignette is persistent and recurrent despite a high glucose infusion rate amounting to 2 mg/kg per minute by enteral route and 16.7 mg/kg per minute by parenteral route for a total of 18.7 mg/kg per min. Failure to resolve hypoglycemia despite a glucose infusion rate that exceeds 12 mg/kg per minute suggests further diagnostic evaluation and additional therapeutic intervention.

Clinical examination of this infant does not suggest excessive utilization of glucose in the peripheral tissues as a cause of hypoglycemia. The laboratory data do not support hyperinsulinism as a cause of hypoglycemia. The plasma cortisol and growth hormone in the lower range of normal suggest that secretion of these counter-regulatory hormones in response to hypoglycemia is insufficient.

The drug most likely to be effective in correcting hypoglycemia in the infant in this vignette is hydrocortisone. This adrenal corticosteroid with primary glucocorticoid effects exerts its therapeutic actions largely by stimulating gluconeogenesis - synthesis of glucose from nonglucose precursors. In addition, hydrocortisone decreases utilization of glucose in the peripheral tissues, stimulates lipolysis, and promotes protein breakdown. The net result is an increase in blood glucose. The dosage of hydrocortisone is 2.5 mg/kg per dose given intravenously or orally at 12-hour intervals. The duration of treatment is guided by the clinical response. The major adverse effects of hydrocortisone include hyperglycemia, hypertension, salt and water retention, increased risk of gastrointestinal perforation, and predisposition to candida sepsis.

Diazoxide is a benzothiadiazine derivative that structurally resembles thiazide diuretics. It is most effective in the treatment of hyperinsulinemic hypoglycemia. It suppresses insulin secretion and augments catecholamine release. Diazoxide inhibits insulin release by acting as a specific ATP-sensitive potassium channel agonist in normal pancreatic beta cells. Additionally, it counters peripheral actions of insulin via catecholamine stimulation. The dosage of diazoxide is 5 mg/kg per dose given orally at 8-hour intervals. Duration of treatment is guided by the clinical response. The major adverse effects of diazoxide include salt and water retention, hyperuricemia, leukopenia/neutropenia, and ketoacidosis. Long-term use is associated with adverse effects of excessive hair growth and coarse facial features. The infant in this vignette does not have hyperinsulinism, which rules out diazoxide as the treatment of choice.

Epinephrine, a sympathomimetic agent with agonist actions on alpha and beta adrenal receptors, is used rarely for the treatment of hypoglycemia, because of its multiple systemic effects. It stimulates hepatic glycogenolysis and decreases glucose utilization in the peripheral tissues, specifically muscle. In addition, epinephrine suppresses insulin secretion and stimulates lipolysis. The preparation used for the treatment of hypoglycemia is an aqueous suspension of 1:200 epinephrine administered subcutaneously. The major adverse effects of epinephrine include cardiac arrhythmia, hypertension with risk of intracranial hemorrhage, renal vascular ischemia, myocardial ischemia, and hypokalemia.

Glucagon is a peptide hormone derived from alpha cells of the pancreatic islets. Its major target tissue is the liver, and its principal action is stimulation of glycogenolysis with release of glucose into circulation. It is least effective as a glycemic agent when the hepatic glycogen stores are depleted, as in the SGA infant in this vignette. Also, by stimulating insulin release, glucagon may have only a transient effect, followed by rebound hypoglycemia. Glucagon is used mostly for the diagnosis of hepatic glycogen storage disease, in which no or minimal increase in blood glucose is seen in response to glucagon. The dosage of glucagon is 200 μg/kg per dose given by intravenous, intramuscular, or
subcutaneous route. The major adverse effects of glucagon include tachycardia, ileus, hyponatremia, and thrombocytopenia.

Octreotide is a long-acting analog of the natural hormone somatostatin. It exerts its glycemic action by inhibiting the secretion of insulin and thus may be used in the treatment of hyperinsulinemic hypoglycemia. Its use, however, is limited because of its multiple hormonal and other effects. Octreotide, in addition to insulin, suppresses growth hormone, glucagon, and thyrotropin. It inhibits the release of several peptides such as serotonin, gastrin, vasoactive intestinal peptide, secretin, and motilin. The dosage of octreotide is 1μg/kg per dose given intravenously or subcutaneously at 6-hour intervals. Dosage and duration of treatment are guided by clinical response. The major adverse effects of octreotide include pulmonary hypertension, steatorrhea, and gastrointestinal dysfunction. The infant in this vignette does not have hyperinsulinism, which contradicts octreotide as the treatment of choice.

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References:


Content Specification(s):

Recognize the approach to therapy and prevention in neonatal hypoglycemia
A 24-hour-old female, whose birthweight is 1180g and estimated gestational age 31 weeks, has jitteriness and hyperreflexia. Maternal history is significant for pregnancy-induced hypertension that worsened despite magnesium treatment and induced vaginal delivery with vertex presentation. Maternal history is negative for sepsis, substance abuse, or other health problems.

The infant's Apgar scores are 7 and 9 at 1 and 5 minutes, respectively. The infant is breathing spontaneously in room air, has no clinical evidence of cardiac dysfunction or birth trauma, and is receiving her own mother's milk by orogastric gavage supplemented with intravenous fluids. Her serum total calcium is 6.2 mg/dL (1.6 mmol/L), with ionized fraction of 3.1 mg/dL (0.8 mmol/L). Her blood glucose is normal, and serum phosphorus, magnesium, parathyroid hormone, and vitamin D test results are pending.

Of the following, the MOST likely cause of hypocalcemia in this infant is:

1. hyperphosphatemia
2. hypocalcitoninemia
3. hypomagnesemia
4. hypoparathyroidism
5. vitamin D deficiency

You selected 1, the correct answer is 4.

The infant in this vignette has early symptomatic hypocalcemia. In term neonates, hypocalcemia is defined as serum total calcium lower than 8 mg/dL (2 mmol/L) or serum ionized calcium lower than 4.4 mg/dL (1.1 mmol/L). These concentrations represent values at 2 standard deviations below the mean of physiologic nadirs in serum calcium at age 24 hours. In preterm neonates, the thresholds for serum calcium used to define hypocalcemia are 7 mg/dL (1.8 mmol/L) for total calcium and 4 mg/dL (1 mmol/L) for ionized calcium.

Hypocalcemia is defined as early if it manifests within 48 hours after birth, and late if it occurs past age 3 to 5 days. The symptoms of hypocalcemia include increased neuromuscular irritability (jitteriness), jerky movements of one or more limbs, and tetany or generalized seizures. The classic signs of hypocalcemia, seen more often in older infants than in neonates, include Chvostek sign - elicited by inducing facial twitching after muscle stimulation - and Trousseau sign - elicited...
by inducing carpal spasm after constriction of the upper arm. Other symptoms of hypocalcemia include apnea and cardiac dysfunction characterized by prolonged QT intervals and arrhythmia.

Early neonatal hypocalcemia occurs with a frequency of 25% to 30% in preterm infants. Hypocalcemia risk increases with the degree of prematurity. Also, the risk is higher among infants of diabetic mothers, infants delivered by cesarean section, infants with birth asphyxia, and infants of mothers taking anticonvulsant medications unsupplemented with vitamin D. Another major risk factor is DiGeorge (velocardiofacial) syndrome, a compilation of aplasia or hypoplasia of parathyroid glands, thymic aplasia with T-cell immune deficiency, and cardiovascular malformations (truncus arteriosus and aortic arch defects). The only risk factor for hypocalcemia in the infant in this vignette is prematurity.

The most common cause of early neonatal hypocalcemia in preterm infants is transient functional hypoparathyroidism. During intrauterine life, the placenta transfers large amounts of calcium and phosphorus to allow fetal skeletal mineralization. The transfer of calcium involves an active placental transcellular mechanism that can overcome maternofetal gradient in calcium concentrations, and also a placental paracellular mechanism that promotes transfer of solutes through water channels. The placental transfer of phosphorus likewise occurs in the maternofetal direction against a concentration gradient.

Much of the transfer of both calcium and phosphorus occurs during the last trimester of pregnancy. Estimates of accretion between 26 and 36 weeks' gestation are 90 to 120 mg/kg fetal body weight per day (2.3 to 3 mmol/kg per day) for calcium and 60 to 75 mg/kg per day (1.9 to 2.4 mmol/kg per day) for phosphorus. Calcium and phosphorus form the major inorganic constituents of bone, with 99% of total body calcium and 80% of phosphorus being in microcrystalline apatite, which deposits in bone only when calcium and phosphorus are simultaneously available in optimal proportions.

At birth, an abrupt interruption of transplacental calcium supply occurs. Regardless of whether the newborn is fed enterally or given intravenous fluids, calcium delivery over the first hours to days after birth does not match calcium delivery during fetal life. This situation sets the stage for a rapid, dramatic decline in serum total and ionized calcium.

Under normal conditions, the decrease in serum ionized calcium stimulates production and secretion of parathyroid hormone (PTH). PTH, in turn, acts directly on the bone, stimulates osteoclast-mediated resorption, and promotes release of calcium into the extracellular fluid and circulation. PTH also acts directly on the kidney to promote urinary retention of calcium and increase urinary excretion of phosphorus. PTH acts indirectly on the gastrointestinal tract by promoting absorption of calcium through its effects on vitamin D metabolism.

In normal term neonates, PTH concentrations, in response to declining serum calcium, increase two- to fivefold in the 48 hours after birth and remain elevated for several days. In preterm neonates, although the parathyroid gland may be capable of secreting PTH, the PTH response to declining serum calcium often is delayed for at least 48 hours after birth. This postnatal latency in elaboration of PTH (transient hypoparathyroidism) prevents hormonal regulation of calcium, and the net result is hypocalcemia. In addition, insufficient calcium intake and immature end-organ responsiveness to PTH from prematurity (functional hypoparathyroidism) may contribute to hypocalcemia.

Hyperphosphatemia is a cause of late hypocalcemia, not early hypocalcemia as in the infant in this vignette. Approximately 80% of total body phosphorus is in the bone, and the remainder is in soft tissues and extracellular fluid. In serum, about two-thirds of phosphorus is organic phosphorus (phospholipids), and one-third is inorganic phosphorus. Of inorganic phosphorus, about 85% is ionized, 5% is complexed to citrate and lactate, and 10% is protein-bound. Serum phosphorus is
not as tightly regulated as serum calcium and shows considerable variation, depending largely on intake and renal excretion. At birth, serum phosphorus ranges from 3.7 to 8.1 mg/dL (1.2 to 2.6 mmol/L); it rises to a peak value averaging 8.2 mg/dL (2.6 mmol/L) about 1 week after birth. This rise is attributed to endogenous release of phosphorus - largely from glycogenolysis and gluconeogenesis - and to low renal excretion of phosphorus.

The rise in serum phosphorus can be exaggerated by both excessive phosphorus and impairment of renal function. Serum phosphorus is inversely related to serum ionized calcium; hyperphosphatemia thus can cause hypocalcemia. Late hyperphosphatemic hypocalcemia, frequently observed in the past in infants fed cow milk or infant formula with high phosphorus content, typically manifests about one week after birth. With current emphasis on human milk feeding and the recent introduction of infant formulas with more balanced calcium and phosphorus content, late hyperphosphatemic hypocalcemia has become rare.

Calcitonin is a peptide hormone secreted by parafollicular cells of the thyroid gland. The synthesis and secretion of calcitonin is influenced primarily by changes in serum ionized calcium. Serum calcitonin increases when serum ionized calcium rises and conversely it decreases when serum ionized calcium falls. The principal action of calcitonin is to decrease serum calcium via its effects on the bone and the kidney. In the bone, calcitonin inhibits osteoclast-mediated resorption and the accompanying release of calcium into circulation. In the kidney, calcitonin promotes urinary excretion of calcium, phosphorus, and magnesium.

In term infants, serum calcitonin at birth ranges from approximately 30 to 240 pg/mL (30 to 240 ng/L). It increases four- to sevenfold within 48 hours of birth and declines thereafter to a steady childhood concentration about age 1 week. In preterm infants, serum calcitonin at birth is higher, ranging from 40 to 280 pg/mL (40 to 280 ng/L), and its rise within the 48 hours after birth is more rapid, pronounced, and sustained. Thus, hypocalcitoninemia is rare in neonates, including preterm infants, and is not a cause of hypocalcemia.

Hypomagnesemia is a cause of persistent hypocalcemia that is refractory to treatment with calcium. Approximately 65% of total body magnesium is in the bone, 34% in the intracellular space, and 1% in the extracellular space. Of the magnesium within the extracellular space, only 25% is in the readily measurable intravascular serum. In the serum, about 55% of magnesium is ionized, 13% is complexed to citrate and lactate, and 32% is protein-bound. Serum magnesium is as tightly regulated as serum calcium. In both term and preterm infants, serum magnesium at birth ranges from approximately 1.5 to 2.5 mg/dL (0.6 to 1 mmol/L). There is an increase in serum magnesium over the first week after birth, followed by a decline toward steady childhood values about age 1 month. Hypomagnesemia, defined as serum magnesium lower than 1.5 mg/dL (0.6 mmol/L), can cause or exacerbate hypocalcemia by inhibiting the parathyroid response to declining serum calcium.

Hypomagnesemia is common among infants of diabetic mothers, infants with birth asphyxia, infants with intrauterine growth restriction, and neonates born to magnesium-deficient mothers. The absence of these risk factors in this vignette makes hypomagnesemia an unlikely cause of hypocalcemia. On the contrary, the infant in this vignette is more likely to have hypermagnesemia resulting from maternal treatment with magnesium. Hypermagnesemia, defined as serum magnesium of more than 3 mg/dL (1.2 mmol/L), is a common iatrogenic result of maternal treatment with magnesium for pregnancy-induced hypertension and preterm labor, and it is not a cause of hypocalcemia.

Vitamin D, either D2 (ergocalciferol) derived from plants or D3 (cholecalciferol) derived from animals, is hydroxylated in the liver to form 25-hydroxyvitaminD [25(OH)D] (Figure). It is hydroxylated further in the kidney to form 1,25-dihydroxyvitaminD [1,25 (OH)2D]. The former is a major circulating metabolite of
vitamin D and is an indicator of vitamin D status. The latter is a biologically active metabolite of vitamin D and acts on the bone, kidney, and intestine to increase serum calcium and phosphorus. Thus, vitamin D deficiency can cause hypocalcemia, which tends to be gradual in development and delayed in its manifestations. Risk factors for vitamin D deficiency include maternal vitamin D deficiency, maternal treatment with anticonvulsants, and limited exposure of the infant to sunshine, as in winter months. The absence of these risk factors in this vignette and the abrupt development of symptoms shortly after birth make vitamin D deficiency an unlikely cause of hypocalcemia.

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References:


Content Specification(s):

Understand the changing requirements of calcium and phosphorus by the neonate at various gestational ages

Understand the etiology and clinical manifestations of neonatal hypocalcemia

Understand the laboratory features and approach to therapy of neonatal hypocalcemia

Understand the etiology, clinical manifestations, and approach to therapy of hypomagnesemia
A 2-day-old infant weighs 1000 g and is at 30 weeks' postmenstrual age. Mother's milk has been started by gavage feedings at 3 mL every 3 hours. You order intravenous alimentation. The hospital pharmacist informs you that pediatric amino acid solutions are in short supply and asks your permission to use an adult solution instead. In comparing the two solutions, you find some significant differences.

Of the following, the amino acid MOST likely to be conditionally indispensable in this child's metabolism is:

- alanine
- lysine
- serine
- tyrosine
- valine

You selected 1, the correct answer is 1.

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In adults, the indispensable amino acids, formerly known as the essential amino acids, are those with carbon skeletons that cannot be synthesized from simpler molecules. They can be remembered using the mnemonic PVT TIM HALL: proline, valine, threonine, tryptophan, isoleucine, methionine, histidine, arginine, leucine, and lysine. All other amino acids are dispensable or conditionally indispensable. As new information comes to light, the amino acid classification scheme changes for adults and infants.

The conditionally indispensable amino acids are those dispensable amino acids whose endogenous synthesis cannot meet the current metabolic need. For example, some severely burned patients require proline in quantities beyond what the body can manufacture. If the "condition" is the very-low-birthweight neonate, the conditionally indispensable amino acids include arginine, cysteine, glycine, tyrosine, and possibly taurine (Figure).
Tyrosine, a dispensable amino acid in adults, is conditionally indispensable in the neonate due to the immaturity of tyrosine aminotransferase and 4-hydroxyphenylpyruvate deoxygenase.

Lysine and valine are indispensable amino acids. Similarly, alanine and serine are dispensable amino acids.

The amino acid solutions used in most neonatal units are designed to achieve plasma amino acid concentration profiles similar to those found in healthy 30-day-old breastfed term infants, or those found in cord blood samples. They differ from solutions used in adults in a number of ways, including having more tyrosine, leucine, isoleucine, lysine, valine, glutamic acid, and taurine. Cysteine is not included in adult or infant amino acid solutions due to storage instability, and must be added just before administration.

References:


Content Specification(s):
Distinguish between indispensable, conditionally indispensable, and dispensable amino acids
The mother of a 25-week-gestation newborn is surprised to learn that she will be able to provide breast milk for her baby despite the premature delivery. You explain to the medical students that the composition of preterm human milk differs in the initial perinatal period from that of term milk.

Of the following, the constituent found in HIGHER concentrations in early preterm human milk as compared to term milk is:

1. beta-casein
2. calcium
3. immunoglobulin A
4. lactalbumin
5. lactose

You selected 3, the correct answer is 3.

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Human milk supplies the newborn with accessible nutrients as well as bioactive and immunoprotective factors. Adapting to the needs of the newborn due to immature function and inadequate endogenous production, human milk provides digestive enzymes, immunoglobulin A (IgA), taurine, nucleotides, and long-chain polyunsaturated fatty acids (LC-PUFAs). Postcolostrum or mature milk is composed of mostly water (88%), followed by carbohydrate (5.6%-6.9%), lipids (3.4%-4.4%), and protein (1.7%-2.2%). Lactose, synthesized within the alveolar cell, is the main carbohydrate, and triglycerides, stored as fat globules, comprise the lipid energy source. The protein constituent of human milk is a mixture of the whey protein lactalbumin, casein, albumin, immunoglobulins, and lysozyme, with a whey-to-casein ratio of approximately 60 to 40 (Table).

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<td>Lactoferrin</td>
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Table. Major Proteins in Human Milk
Free amino acids and compounds, such as urea, comprise a small nonprotein nitrogen component.

In addition to providing a nutrient source, human milk proteins function in the immune and nonimmune protection of the newborn from infection. Fourfold higher in colostrum than mature milk, IgA is the main immunoglobulin component and is resistant to proteolysis. The protective effect of IgA is mainly at the mucosal surface, playing an important role in first-line epithelial defense. Nonimmune protection is provided by many milk proteins. Lactoferrin is bactericidal, antiviral, and anti-inflammatory, and modulates cytokine function. Lysozyme, the only protective protein that increases in concentration throughout lactation, cleaves bacterial walls and lyses gram-positive and some gram-negative bacteria.

The constituents of human milk change over the course of lactation, with milk considered mature by two to three weeks. Colostrum, produced over the first four to five days of lactation, is richer in protein than mature milk, particularly due to a greater concentration of immunoglobulins. During the first month, the protein content rapidly decreases, reaching a nadir by 6 months. The lactose and albumin content remain relatively constant. Over time, the lipid content increases and remains the most variable component of human milk. During an individual feeding, the energy content of mature milk changes, with the fat content of hindmilk being two- to threefold higher than that of foremilk (supplying 25 to 35 kcal/100 mL more energy on average).

The composition of the breast milk of a mother of a preterm infant (preterm milk) differs from that of a full-term infant, particularly during the first two weeks of lactation. The protein content of preterm milk is twice that of term milk, containing 2.0 g/100 mL at one week. Preterm milk has been shown to contain twice as much IgA, but also increased concentrations of lactoferrin and lysozyme compared with term milk, thus adapting to the increased immunologic needs of the preterm infant. The absolute concentration of the nutritional proteins beta-casein and lactalbumin is initially lower in preterm than term milk. After a few weeks, the nutritional proteins increase and immunological constituents decrease to concentrations of term milk. Preterm milk contains less lipid overall, but elevated concentrations of LC-PUFAs, which are essential for physical growth, brain development, and retinal function. Lactose concentrations are found to be decreased or unchanged. Differences in other nutrients exist as well, with preterm milk having equal or lower concentrations of calcium and phosphorus, but a higher sodium content than term milk.

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References:


**American Board of Pediatrics Content Specification(s):**

Know the difference between the composition of the breast milk of the mother of a preterm infant and that of a full-term infant.
March: Question 1

An elderly primagravida has amniocentesis showing fetal chromosomes of 46XX. Fetal ultrasound suggests enlarged adrenal glands. After birth at term, the child has cliteromegaly and posterior labial fusion. Over the next week, the infant's blood pressure increases, reaching 120 mm Hg systolic by day 10.

Of the following, the MOST likely diagnosis is:

1. 3-beta-hydroxysteroid dehydrogenase deficiency
2. 11-beta-hydroxylase deficiency
3. 17-alpha-hydroxylase deficiency
4. 20,22-desmolase deficiency
5. 21-hydroxylase deficiency

You selected 4, the correct answer is 2.

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The pathway from cholesterol to cortisol comprises five enzymatic steps (Figure): 20,22-desmolase, 17-alpha-hydroxylase (17-OH), 3-beta-hydroxysteroid dehydrogenase (3-beta-HSD), 21-hydroxylase (21-OH), and 11-beta-hydroxylase (11-OH).
Impairment of any one of these five steps results in a deficiency of cortisol and a subsequent surfeit of adrenocorticotropic hormone (ACTH), which then leads to adrenal hyperplasia. The overproduction of precursor steroids before a specific blockage causes most of the signs of that specific disorder. The disorder most associated with virilization in the female and hypertension is a deficiency of 11-OH.

Deficiency of 11-OH, representing about 5% of cases of congenital adrenal hyperplasia, results in a build up of deoxycorticosterone (DOC), which has a mineralocorticoid effect. The enhanced salt retention causes low-renin hypertension. An excess of androgens leads to virilization of the female fetus, as in the vignette. Increased concentrations of 11-deoxycortisol (compound S) and DOC suggest the diagnosis. Treatment with glucocorticoids is monitored using plasma renin activity, blood pressure, and serum concentrations of 11-deoxycortisol and DOC.

Deficiency of 21-OH represents over 90% of cases of congenital adrenal hyperplasia. The disorder is autosomal recessive, as are each of the five disorders, with an incidence of 1 in 15,000 neonates in most state screening programs. Incidence is greater among some ethnic groups, as high as 1 in 282 among the Yupik Inuits in Alaska. The most common form involves loss of salt in the first few weeks after birth, due to the lack of aldosterone, and can present as hypovolemic shock. Hyperkalemia, lethargy, weight loss, hypoglycemia, metabolic acidosis, and seizures may occur. Cardiovascular effects of hypocortisolemia include decreases in cardiac output, vascular tone, and blood pressure. Build up of dehydroepiandrosterone (DHEA) and androstenedione causes virilization in females.

The diagnosis of 21-OH deficiency in neonates is indicated by high concentrations of 17-OH-progesterone (17-OHP). Treatment includes volume and glucose stabilization followed by long-term glucocorticoids (often oral hydrocortisone) and
mineralocorticoids (eg, fludrocortisone). Treatment efficacy is assessed by monitoring concentrations of 17-OHP, androstenedione, and plasma renin activity. Prenatal diagnosis of 21-OH deficiency is available via amniotic fluid 17-OHP, human lymphocyte antigen (HLA) matching of the fetus with an index case within the family (taking advantage of the linkage of this gene with the HLA complex), or direct DNA analysis of the fetus if the DNA abnormality in the index case is known. In utero treatment of the fetus at risk, with small doses of maternal dexamethasone to suppress fetal ACTH and limit virilization, begins ideally before a fetal age of 6 weeks. Treatment continues until the sex is proven to be 46XY male or the fetus is proven not to have the disorder. Newborn screening programs test for 17-OHP. Forms of congenital adrenal hyperplasia without elevated concentrations of 17-OHP will not be detected by newborn screening.

Deficiency of 3-beta-HSD prevents production of glucocorticoids, mineralocorticoids, and sex steroids. Lack of cortisol and aldosterone causes salt-losing adrenal crises. Males may have severe hypospadias from the testosterone deficiency. Elevation of DHEA concentration can cause mild virilization of females secondary to the androgens made by hepatic 3-beta-HSD, under separate genetic control. Glucocorticoid and mineralocorticoid treatment is assessed by monitoring concentrations of 17-OH-pregnenolone and DHEA and plasma renin activity.

Deficiency of 17-OH presents with hypertension and hypogonadism. Cortisol, androgens, and estrogens are reduced. Increased DOC and corticosterone lead to low-renin hypertension, and their glucocorticoid properties prevent adrenal insufficiency. 46XX female infants have normal genitalia, but do not develop normally during puberty. 46XY males may be phenotypically female with undescended testes and inguinal hernias, or may have ambiguous genitalia. Glucocorticoid treatment is given, but mineralocorticoid treatment is not needed.

Deficiency of 20,22-desmolase, also called congenital lipoid adrenal hyperplasia, inhibits production of all adrenal and gonadal steroids and leads to an accumulation of cholesterol and lipid in the adrenals that is characteristic. Patients present with adrenal crises including sodium wasting, hypoglycemia, and hyperpigmentation. Males may have female genitalia, including a blind vaginal pouch, or ambiguous genitalia. Females have normal genitalia.

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**References:**


**American Board of Pediatrics Content Specification(s):**

Recognize the clinical manifestations and laboratory features of the various types of congenital adrenal hyperplasia
Define the appropriate therapy of the various types of congenital adrenal hyperplasia
June: Question 10

A 5-day-old male infant born at 33 weeks' gestation is feeding poorly. Half of his fluid intake is provided parenterally. Findings on physical examination are normal except for lethargy. Laboratory findings include a total serum calcium concentration of 14 mg/dL (3.5 mmol/L).

Of the following, the MOST likely cause of this child's hypercalcemia is:

1. blue diaper syndrome
2. familial hypocalciuric hypercalcemia
3. iatrogenic hypercalcemia
4. maternal hypoparathyroidism
5. Williams syndrome

You selected 5, the correct answer is 5.

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Neonatal hypercalcemia is most often defined as a total serum calcium concentration of more than 11.0 mg/dL (2.75 mmol/L) or a plasma ionized calcium concentration of more than 5.4 mg/dL (1.35 mmol/L). Symptoms may include failure to thrive, anorexia, poor feeding, lethargy, hypotonia, vomiting, or constipation. Rare findings include seizures, bradycardia, or hypertension.

The causes of neonatal hypercalcemia can be arranged according to the clinical approach (Table).
Iatrogenic hypercalcemia, often the result of excessive parenteral calcium administration, is the most common cause of early-onset hypercalcemia, as is likely in the infant in the vignette. A review of fluid orders and analysis of the intravenous fluid may explain the root cause for excess intake and avoid unnecessary testing.

Other potential iatrogenic sources of excess calcium administration include calcium provided during exchange transfusion or extracorporeal membrane oxygenation. Vitamin D intoxication causes excess intestinal absorption of calcium and phosphorus. Vitamin A intoxication can result in increased bone turnover and release of calcium into the blood. Both vitamin A and vitamin D intoxications are associated with excess administration of the vitamin, not likely to have occurred in the infant in the vignette. Insufficient provision of phosphorus in parenteral nutrition or oral formulas increases intestinal absorption of calcium while preventing calcium deposition in the bones, leaving excess calcium in the serum. Thiazide diuretics reduce renal calcium excretion and can be associated with high serum calcium concentrations.

Treatment of hypercalcemia starts with restriction of calcium and vitamin D intake, and should be sufficient for situations such as that seen in the vignette. Urinary excretion may be encouraged by the use of intravenous saline and, once rehydration is achieved, a loop diuretic such as furosemide. Glucocorticoids, calcitonin, bisphosphonate, or dialysis may be needed in special cases. Treatment can be monitored using calcium, phosphorus, and parathyroid hormone levels. Renal ultrasonography aids in monitoring nephrocalcinosis.

Neonatal hypercalcemia occurs less frequently as a result of insufficiently treated maternal hypoparathyroidism than of iatrogenic causes. The low maternal calcium concentration is mirrored in the fetus because of low transplacental calcium transfer. The low fetal calcium concentration stimulates the fetal parathyroid glands, which then persist after birth to produce a surfeit of parathyroid hormone. The excess parathyroid hormone keeps the serum calcium concentration high by mobilizing calcium and phosphorus from bone, and by enhancing the renal reabsorption of calcium. The production of excess parathyroid hormone is transient, and any bone abnormalities usually resolve within 6 months.
Familial hypocalciuric hypercalcemia is a rare heterozygous autosomal dominant defect in the calcium-sensitive receptors of the parathyroid glands and the kidneys. The calcium-sensing "set-point" in these organs is elevated, so that a higher serum calcium concentration is needed to inhibit parathyroid hormone production, or to inhibit renal calcium reabsorption. In these children, the concentration of parathyroid hormone is inappropriately normal despite the hypercalcemia. Renal calcium excretion is impaired, with resulting hypocalciuria. Treatment is based on the severity of any symptoms; most patients are asymptomatic.

The same gene defect of the calcium-sensitive receptors of the parathyroid glands and the kidneys, when homozygous, causes neonatal severe hyperparathyroidism. Complete insensitivity of the parathyroid glands to any calcium level results in high parathyroid concentrations, and calcium concentrations are often in the range of 15 mg/dL to 30 mg/dL (3.75-7.5 mmol/L). The condition is life threatening with a mortality rate of 25 percent. Treatment often includes total parathyroidectomy.

The blue diaper syndrome is a rare disease. A defect in tryptophan transport causes intestinal accumulation and bacterial production of indole, which is absorbed, processed, and excreted in the urine as indigotin (indigo blue). The cause of the associated hypercalcemia, which often presents as a failure to thrive, is unknown. Treatment involves a diet low in calcium and vitamin D, and glucocorticoids.

Williams syndrome comprises elfin facies (epicanthal folds, medial eyebrow flare, anteverted nares, prominent maxillae, small mandible, prominent lips), cardiac abnormalities (supravalvular aortic stenosis), "cocktail party" personality (mental retardation with loquaciousness), and hypercalcemia. It usually is caused by a sporadic microdeletion of chromosome 7. The hypercalcemia is transient and self-resolving. Treatment initially consists of a low calcium and low vitamin D diet. The mechanism of the hypercalcemia is unknown.

References:


American Board of Pediatrics Content Specification(s):

Understand the etiology and clinical manifestations of neonatal hypercalcemia

Understand the laboratory features and approach to therapy of neonatal hypercalcemia
You are called to examine an infant in the delivery room because of “ambiguous genitalia.” The infant's 38-year-old mother is a gravida 3, para 3 0 0 3. She underwent amniocentesis during pregnancy, showing the fetus to be 46,XY. On examination, the infant is found to have a small phallus with the urethral meatus at the tip. Small gonads are palpable in the scrotum (Figure 1).

Figure 1

In the mother's room at 5 hours of age, the infant is noted to be jittery. His blood glucose concentration is 15 mg/dL (0.8 mmol/L).

Of the following, the hormone deficiency MOST likely to be primarily responsible for the genital findings in this infant involves:

1. adrenal androgen
2. chorionic gonadotropin
3. cortisol
4. luteinizing hormone
5. thyroxin

You selected 2, the correct answer is 1.
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The infant in this vignette has micropenis. Micropenis is defined as having stretched penile length of less than 2.5 cm in the term infant. Penile length is measured from the pubic ramus to the tip of the glans using gentle traction. Mean penile length at term is 3.5 cm. When evaluating preterm infants of 24 to 36 weeks’ gestation, the following formula gives approximate mean penile length:

Penile Length (centimeters) = 2.27 + (0.16 × [Gestational Age in Weeks])

The graph represents penile length (mean and 2 standard deviations below the mean) at 30 to 40 weeks’ gestation (Figure 2).

![Figure 2: Penile Length (cm)](image)

Some male infants have a prominent pad of prepubic fat overlying a normal-length penis, the length of which can easily be determined by palpation. Parental reassurance is important in this situation.

Important to this evaluation is the presence of the urethra at the tip of the phallus, labioscrotal fusion, and the presence of gonads. During male fetal development, human chorionic gonadotropin binds to the luteinizing hormone (LH) receptor in the testes, resulting in the release of testosterone. This testosterone is then converted to the more active dihydrotestosterone (DHT), which mediates the differentiation and stabilization of the internal and external genitalia, resulting in formation of a normal penis. At about 14 weeks’ gestation, LH production shifts from the placenta to the fetus. In the absence of fetal hypothalamic-pituitary production of LH, testosterone (and DHT) production will be insufficient and the normally formed penis will fail to grow, as depicted by the infant in this vignette. Micropenis in the absence of other genital ambiguity is most likely mediated by insufficient secretion of LH because of insufficient hypothalamic production of gonadotropin-releasing hormone (GnRH) or underproduction of LH by the anterior pituitary, with resultant low testosterone (and DHT) secretion.

Idiopathic hypogonadotropic hypogonadism (IHH) results most commonly from the absence of GnRH secretion by the hypothalamus. It is the most common cause of secondary hypogonadism. Males constitute over 90% of cases, and IHH is the cause of one half of all cases of micropenis. Affected females have no phenotypic abnormality in the newborn period. Low concentrations of LH and follicle-stimulating hormone support the diagnosis. Associated features of midline defects (cleft lip or palate), renal agenesis, cryptorchidism, and (later in life) anosmia should be sought. If accompanied by anosmia, the condition is called Kallmann syndrome. Two thirds of cases are sporadic. Inheritable forms have been autosomal dominant,
autosomal recessive, and X-linked. In the X-linked form, impaired migration of GnRH neurons from the olfactory placode to the hypothalamus has been documented. This migration is mediated by anosmin-1, the gene for which is located at Xp 22.3. Gene defects have not been consistently found in the other forms of inherited GnRH deficiency and are rarely documented among sporadic cases.

Some cases of micropenis may be associated with hypopituitarism, with deficient concentrations of growth hormone (which plays a role in penile growth), gonadotropins, thyroid-stimulating hormone, and adrenocortical-stimulating hormone. Evaluations for hypoglycemia and of thyroid and adrenal function should accompany any diagnosis of micropenis. Low blood sugar in the infant in the vignette suggests the need for this evaluation.

Failure of conversion of testosterone to DHT (5-alpha reductase deficiency) and androgen receptor abnormalities also may result in micropenis, but incomplete labioscrotal fusion also is seen because DHT insufficiency influences early fetal genital differentiation (Figure 3).

Micropenis has been described in many genetic syndromes, and its presence should lead to detailed overall examination. It is frequently present in patients with anencephaly, Borjeson-Forssman-Lehmann, Carpenter, CHARGE, Johanson-Blizzard, Meckel-Gruber, Noonan, Pallister-Hall, popliteal pterygium, Prader-Willi, Robinow, Saldino-Noonan, and X-linked alpha-thalassemia/mental retardation syndromes. It has also been noted among patients having 9p deletion, 18q deletion, trisomy 9 mosaicism, XXXXY and XXY karyotypes.

Treatment depends on the underlying diagnosis. Male patients with low gonadotropin levels may respond to androgen treatment, with penile growth approaching normal ranges. Some infants with varying degrees of androgen insensitivity may be better raised as females. The complexity of the decision-making process requires expert endocrinological consultation and follow-up.

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References:


American Board of Pediatrics Content Specification(s):
Know the importance of the combination of micropenis and hypoglycemia

Know how to evaluate and manage an infant with micropenis
August: Question 8

You are consulting with a mother whose pregnancy is complicated by intrauterine growth restriction (IUGR). The mother is healthy without risk factors for IUGR and the pregnancy has been otherwise uncomplicated. No IUGR cause has been identified. No anomalies are evident on fetal and placental ultrasonography or suggested by antenatal quadruple screening. During your discussion with the woman, her family, and the care team, you describe the transfer of nutrients (including fats, carbohydrates, and amino acids) to the fetus and deficiencies that may contribute to IUGR.

Of the following, the MOST important mechanism for amino acid uptake by the fetus is:

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>1</td>
<td>active transport</td>
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<tr>
<td>2</td>
<td>diffusional transfer</td>
</tr>
<tr>
<td>3</td>
<td>facilitated diffusion</td>
</tr>
<tr>
<td>4</td>
<td>paracellular diffusion</td>
</tr>
<tr>
<td>5</td>
<td>receptor-mediated endocytosis</td>
</tr>
</tbody>
</table>

You selected 1, the correct answer is 1.

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The fetus receives nutrients, ions, water, and immunoglobulins to support growth, metabolism, and resistance to infection. The mechanisms for transfer of these important molecules remain the subject of investigation, and much information is derived from comparative biological studies in humans, sheep, rats, rabbits, and guinea pigs.

Uptake of amino acids for fetal growth and energy production depends on transporter proteins that involve hydrolysis of adenosine triphosphate, or active transport. This process is complex because of the existence of many different transport proteins, changes in the ontogeny of transport systems during gestation, secondary active transport (an amino acid may cotransport or be exchanged with another solute or amino acid), net flux of amino acids from the fetus to the placenta (aspartate, glutamate, serine), and net flux of amino acids from the placenta to the fetus.

Amino acid uptake is affected by the presence of placental abnormalities associated with fetal growth restriction (reduced villous surface area, altered transporter number and activities, and decreased placental perfusion), uterine and umbilical blood flow, and amino acid cycling between the placenta and fetal liver (especially alanine; serine; glutamate; and the branched chain amino acids leucine, isoleucine, and valine). Furthermore, maternal amino acid concentrations influence fetal amino acid uptake. The uptakes of some, but not all, amino acids are increased by increasing maternal amino acid concentrations. A better understanding of the processes involved in fetal uptake of individual amino acids will provide insights into the
benefits and safety of maternal nutrient supplementation, especially when fetal growth restriction occurs (as in the infant in the vignette).

Molecules also diffuse along a maternofetal concentration gradient without transport proteins (diffusional transfer). The net rate of diffusional transfer of a given solute or molecule through the placenta from the maternal to the fetal circulation is described by Fick's law, as follows:

\[ J_{\text{net}} = PS (c_m - c_f) \]

Where \( J_{\text{net}} \) is the net rate of uptake (mol sec\(^{-1}\) g placenta\(^{-1}\)); \( P \) is the proportionality constant (placental permeability, cm\(^2\)sec\(^{-1}\)); \( S \) is the surface area available for diffusion between circulations within 1 g of placenta (cm\(^2\)g\(^{-1}\)); and \( c_m \) – \( c_f \) is mean plasma solute concentrations (mol cm\(^{-3}\)) of the unbound solute in plasma water in maternal (\( c_m \)) and fetal blood (\( c_f \)) flowing past the exchange area.

Fick's law states that the net uptake of a solute is proportional to placental permeability, surface area, and the maternofetal concentration difference. The net uptake is also a function of lipid solubility, net charge, and size of the solute or molecule, and fetal and maternal blood flow.

Facilitated diffusion is saturable and stereospecific, shows competition, and is independent of energy sources. The energy required to move nutrients is derived from electrochemical gradients. Glucose transfer occurs by facilitated diffusion at the microvillus and basal plasma membrane of the syncytiotrophoblast.

Lipid-soluble substances (such as respiratory gases) diffuse through the entire trophoblastic surface area and are not limited by permeability. Rather, flow limitation by the fetal and maternal blood flows most affects transfer. Because of significant reserves, flows must be significantly limited to reduce fetal uptake.

Lipid-insoluble substances (such as sodium and mannitol) move through placental barriers slowly because of limited surface area and permeability. Thus, lipid-insoluble molecules are described as being membrane limited. Lipid-insoluble molecules enter the fetal circulation through transcellular routes and, possibly, extracellular pores. Paracellular diffusion through extracellular pores is another route for lipid-insoluble molecules to cross from the maternal to fetal circulation.

Receptor-mediated endocytosis is an invagination of the cell surface to form an intracellular membrane-bound vesicle. Phagocytosis, or ingestion of large particles, and pinocytosis, or ingestion of water and small molecules, describe two different categories of endocytosis. Immunoglobulin G (IgG), transferrin/iron, and low-density lipoproteins enter the syncytiotrophoblast by endocytosis. IgG binds to specific Fc receptors in clathrin-coated pits in specialized regions of the cell membrane. Endocytosis forms microvesicles that do not fuse with lysosomes and selectively transfers IgG across the human syncytiotrophoblast.

References:


American Board of Pediatrics Content Specification(s):
Know the role of the placenta in the energy metabolism of the fetus, including transfer of glucose, electrolytes, and amino acids to the fetus

Understand the implications and management of fetal growth restriction
A 3-day-old male infant whose birthweight was 680 g and estimated gestational age at birth 24 weeks has lethargy and decreased muscle tone. Maternal history was significant for spontaneous preterm labor and cesarean section delivery for fetal breech presentation. The infant’s Apgar scores were 7 and 8 at 1 and 5 minutes after birth, respectively. After treatment with two doses of surfactant, the infant continues to receive ventilator support with a fraction of inspired oxygen of 0.28. The infant is receiving parenteral nutrition (glucose: 7.5 g/dL, protein: 2.0 g/dL, lipid: 1.0 g/dL, calcium: 40 mg/dL, and phosphorus: 10 mg/dL) at a rate of 120 mL/kg per day. Enteral feeds are not yet started. Physical examination reveals an immature infant with normal vital signs and no anomalies or dysmorphic features. The infant is receiving no medications other than antibiotics.

Laboratory data reveal the following:

- serum total calcium 12.8 mg/dL (3.2 mmol/L)
- serum ionized calcium 6.4 mg/dL (1.6 mmol/L)
- serum phosphorus 3.1 mg/dL (1.0 mmol/L)
- serum sodium 138 mEq/L (138 mmol/L)
- serum potassium 4.0 mEq/L (4.0 mmol/L)
- serum chloride 100 mEq/L (100 mmol/L)

Arterial blood gas reveals the following:

- pH 7.23
- partial pressure of carbon dioxide 42 mm Hg (5.6 kPa)
- partial pressure of oxygen 74 mm Hg (9.9 kPa)
- plasma bicarbonate 17 mEq/L (17 mmol/L)
- plasma base deficit 10 mEq/L (10 mmol/L)

Of the following, the MOST appropriate treatment for this infant is to:

1. add cysteine to parenteral nutrition
2. administer calcitonin
3. administer furosemide
4. increase phosphorus in parenteral nutrition
5. remove calcium from parenteral nutrition

You selected 1, the correct answer is 1.

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The young, extremely low-birthweight infant in this vignette has early acute hypercalcemia. In neonates, hypercalcemia is defined as a serum total calcium concentration in excess of 11.0 mg/dL (2.8 mmol/L). The corresponding threshold for serum ionized calcium concentration is 5.5
mg/dL (1.4 mmol/L). The hypercalcemia may be defined as early if it manifests within the transitional period shortly after birth, and late if its occurrence is delayed beyond the first week of age. Typically, early hypercalcemia is acute and transient, whereas late hypercalcemia can be chronic and often accompanied by long-term consequences such as metastatic calcification, primarily nephrocalcinosis. Neonatal hypercalcemia can be asymptomatic, or it may manifest with nonspecific signs such as bradycardia, decreased muscle tone, lethargy, polyuria, and poor feeding.

The causes of early acute hypercalcemia include excessive administration of calcium or vitamin D, use of calcium-retaining thiazide diuretics, and prostaglandin excess. A more common, but underrecognized, cause of early acute hypercalcemia, particularly in preterm neonates, is phosphorus deficiency (hypophosphatemic hypercalcemia).

The causes of late chronic hypercalcemia include congenital hyperparathyroidism, idiopathic infantile hypercalcemia, Williams syndrome (elfin facies, supravalvular aortic stenosis, peripheral pulmonic stenosis, motor disability, mental retardation, dental abnormalities, and microdeletion on chromosome 7 involving the elastin gene), subcutaneous fat necrosis, hyperprostaglandin E syndrome (Bartter syndrome), infantile hypophosphatasia, and familial benign hypocalciuric hypercalcemia.

The normal range of serum phosphorus concentration in neonates is 4.5 to 9.3 mg/dL (1.5-3.0 mmol/L). Based on this range, the infant in this vignette has hypophosphatemic hypercalcemia. To understand the development of this disorder, it is important to examine the fetal metabolism of calcium and phosphorus.

During intrauterine life, the placenta transfers large amounts of calcium and phosphorous to support fetal skeletal mineralization. The transfer of calcium involves an active placental transcellular mechanism that can overcome the maternofetal gradient in calcium concentrations. The placental transfer of phosphorus, likewise, occurs in the maternofetal direction against a concentration gradient. Much of the transfer of both calcium and phosphorus occurs during the last trimester of pregnancy. Estimates of accretion during this period are 90 to 120 mg/kg of fetal bodyweight per day (2.3-3.0 mmol/kg per day) for calcium and 60 to 75 mg/kg per day (1.9-2.4 mmol/kg per day) for phosphorus. The calcium and phosphorus form the major inorganic constituents of bone, with 99% of total body calcium and 80% of phosphorus being in the microcrystalline apatite, which forms in the bone only when calcium and phosphorus are available simultaneously and in optimal proportions. The optimal ratio of calcium to phosphorus administration is estimated to be 2:1.

In the infant in this vignette, the intake of phosphorus (12 mg/kg per day [0.4 mmol/kg per day]) and calcium (48 mg/kg per day [1.2 mmol/kg per day]) amounts to far less than the rates of fetal acquisition. Moreover, the calcium to phosphorus ratio of 4:1 indicates a marked deficiency in the intake of phosphorus relative to the intake of calcium. In phosphorus deficiency, the incorporation of calcium in the bone is limited, which results in accumulation of calcium in the extracellular fluid and hence an increase in serum calcium concentration. The appropriate treatment for the infant in this vignette is to increase the phosphorus intake by adding to parenteral nutrition and to achieve a calcium to phosphorus ratio that approximates 2:1. The deficient intake of calcium in this infant does not warrant removal of calcium from parenteral nutrition.

A major barrier to the delivery of optimal amounts of calcium and phosphorus via parenteral nutrition is the poor solubility of the mineral salts. Greater solubility of calcium and phosphorus can be achieved largely by lowering the pH of the parenteral nutrition solution, either by adding cysteine hydrochloride and/or by raising the amino acid concentration. Cysteine, an essential amino acid for preterm infants, is not soluble in current parenteral nutrition solutions and is added in the form of cysteine hydrochloride. One of the side effects of cysteine hydrochloride is metabolic acidosis. The arterial blood gas in the infant in this vignette shows metabolic acidosis, which can be aggravated by cysteine hydrochloride. Thus, although high intakes of both calcium and phosphorus are important in the nutritional treatment of preterm neonates, the addition of cysteine hydrochloride to achieve that goal may need to be delayed pending resolution of metabolic acidosis in this infant.
Calcitonin is a peptide hormone secreted by parafollicular cells of the thyroid gland. The synthesis and secretion of calcitonin is influenced primarily by changes in serum ionized calcium concentration. The serum calcitonin concentration increases when serum ionized calcium rises and conversely it decreases when serum ionized calcium falls. The principal action of calcitonin is to decrease serum calcium concentration via its effects on the bone and the kidney. In the bone, calcitonin inhibits osteoclast-mediated resorption and accompanying release of calcium into circulation. In the kidney, calcitonin promotes urinary excretion of calcium, phosphorus, and magnesium. In term infants, the serum calcitonin concentration at birth ranges from 30 to 240 pg/mL (30-240 ng/L). It increases 4- to 7-fold within the first 48 hours after birth and declines thereafter to reach a steady childhood concentration by about 1 week of age. In preterm infants, the serum calcitonin concentration at birth is higher, ranging from 40 to 280 pg/mL (40-280 ng/L), and its rise within the first 48 hours after birth is more rapid, pronounced, and sustained. Hypocalcitoninemia is rare in neonates, including preterm infants, and is not the cause of hypercalcemia. Administration of calcitonin is not warranted in the infant in this vignette.

Furosemide, a potent loop diuretic, can increase calcium excretion in the urine and lower serum calcium concentration. Its use, however, is limited to chronic and potentially life-threatening elevations in serum calcium concentration.

References:


American Board of Pediatrics Content Specification(s):

Understand the normal calcium, phosphorus, and magnesium metabolism during the perinatal period, including fetal accretion rates

Understand the interrelated effects of various hormones, including parathormone, calcitonin, and vitamin D on calcium, phosphorus, and magnesium metabolism in the fetus and neonate

Understand the etiology and clinical manifestations of neonatal hypercalcemia

Understand the laboratory features and approach to therapy of neonatal hypercalcemia
A physician has been called to the delivery of an infant born to a 43-year-old gravida 6, para 4 mother. At the delivery, it is difficult to determine the sex of the infant from the external genitalia; however, because the mother has had amniocentesis you know that the chromosomes are 46,XX. A previous male sibling died before age 1 month of unknown causes 15 years ago.

Of the following, the enzyme deficiency MOST likely to be responsible for the problems of both siblings is:

- 3ß-hydroxysteroid dehydrogenase
- 11ß-hydroxylase
- 17a-hydroxylase
- 20,22 desmolase
- 21-hydroxylase

You selected 1, the correct answer is 5.

Do you want to add anything to your Learning Plan?
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The siblings in the vignette most likely have congenital adrenal hyperplasia with salt wasting. Fifteen years ago, screening for congenital adrenal hyperplasia was far less common and infants were identified clinically, if at all. A deficiency of any of the five enzymes among the answer choices would cause congenital adrenal hyperplasia. With a deficiency of each of these, the production of cortisol, the main suppressor of adrenocorticotropic hormone (ACTH) secretion is interrupted (Figure 1).

Figure 1: Glucocorticoid biosynthesis
In response to an outpouring of ACTH, the adrenal gland is stimulated to produce steroid hormones, and adrenal hyperplasia occurs. As a result, an excess of cortisol precursors with androgenic actions is secreted, leading to virilization and ambiguous external genitalia in the female fetus. This is manifested by abnormal enlargement of the clitoris, genital and areolar hyperpigmentation, and fused and/or rugated labia majora. Boys with congenital adrenal hyperplasia tend to be overlooked, because the effects of the excess androgens might not produce abnormal physical findings other than some hyperpigmentation.

The nomenclature for the enzymes listed has evolved over time and synonyms are listed in the Table.

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<thead>
<tr>
<th>Common Name</th>
<th>Synonym(s)</th>
<th>Gene</th>
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<td>11β-hydroxylase</td>
<td>Cytochrome P450C11B1 oxygenase</td>
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<tr>
<td>17α-hydroxylase</td>
<td>Cytochrome P450C17 oxygenase</td>
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<td>Cholesterol side-chain cleavage enzyme complex, cytochrome P450ssc</td>
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<td>3β-HSD</td>
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</table>

Deficiency of 21-hydroxylase underlies 90% of cases of congenital adrenal hyperplasia and occurs in 1 in 15,000 live births. Infants who have a deficiency of 21-hydroxylase present with one of two syndromes: partial deficiency with virilization only and severe deficiency with virilization and salt wasting. In both types of 21-hydroxylase deficiency, the block in cortisol production results in high ACTH concentrations that stimulate the adrenal glands to produce androgens. 21-hydroxylase does not play a role in sex hormone production (Figure 2).
Figure 2: Androgen and estrogen biosynthesis

21-hydroxylase is a necessary enzyme in the synthesis of the mineralocorticoids, desoxycorticosterone, and aldosterone (Figure 3).

Figure 3: Mineralocorticoid biosynthesis

These hormones function to increase reabsorption of sodium from the distal tubules of the kidney in exchange for hydrogen ions and potassium. In their absence, large quantities of sodium are lost in urine. Male infants with congenital adrenal hyperplasia and salt wasting are usually sent home after birth with no apparent abnormality only to return with hyponatremia, hyperkalemia, metabolic acidosis, and shock. The onset of this adrenal crisis is usually after 6 days and before 1 month of age and may be confused with septic shock. The female infant in the vignette had evidence of virilization (ambiguous genitalia) and the previous male infant succumbed to an unknown illness around the time expected for salt-losing adrenal hyperplasia.

Infants with 3ß-hydroxysteroid dehydrogenase deficiency have decreased production of all three classes of adrenal steroids (Figure 4).
This form of congenital adrenal hyperplasia is rare. Both sexes can display external genital ambiguity. Males often have severe hypospadias and females have minimal virilization. Salt-losing adrenal crises are also seen.

Infants with congenital adrenal hyperplasia resulting from a deficiency of 11ß-hydroxylase are virilized and have low-renin hypertension. This disorder accounts for 5% of cases of congenital adrenal hyperplasia and occurs in 1 in 100,000 live births. The hypertension results from sodium retention stimulated by an excess production of desoxycorticosterone, which although not as potent as aldosterone, does produce sodium retention when overproduced (Figure 3). Early death is uncommon.

Deficiency of 17α-hydroxylase appears clinically as hypertension and hypogonadism. These individuals are unable to produce cortisol and sex hormones. The increased ACTH stimulation leads to high concentrations of desoxycorticosterone and progesterone. Genetic females have normal genitalia at birth but fail to develop secondary sexual characteristics at puberty. XY males can appear to be female, with a distal vagina and undescended testes at birth, but can also be variably masculinized.

Deficiency of 20,22 desmolase is also known as congenital lipoid adrenal hyperplasia. Infants with this condition are unable to produce all types of adrenal steroids: glucocorticoids, mineralocorticoids, and sex steroids. It is a rare but serious disease that can lead to death in the first few months after birth, with salt wasting and hypoglycemia. Genetic females appear normal. Genetic males have ambiguous external genitalia often with a distal vagina and undescended testes. The adrenal glands are engorged with a large accumulation of lipids.

References:


American Board of Pediatrics Content Specification(s):

Understand the etiology of electrolyte abnormalities in the neonate

Understand the etiologies of abnormal sexual differentiation

Know the etiology and diagnosis of an infant with ambiguous genitalia, including congenital adrenal hyperplasia

Know the clinical manifestations of an infant with ambiguous genitalia, including congenital adrenal hyperplasia

Know the clinical manifestations and laboratory features of the various types of congenital adrenal hyperplasia
You are asked to see a female infant at 72 hours of age who is unresponsive and tachypneic. She was born at term after an uneventful pregnancy and appeared healthy. She had been mildly tachypneic the previous day. Blood culture is sterile 30 hours later. Complete blood counts and C-reactive protein concentrations are normal. After several hours of progressive lethargy, tachpnea, and poor feeding, she has become comatose. Blood gases show a mild respiratory alkalosis; no ketones are present in the urine; no anion gap is present. Blood sugar is normal. Blood ammonia concentration is 1,351 μg/dL (965 μmol/L).

Of the following, the condition MOST consistent with these findings is:

1. arginase deficiency
2. citrin deficiency
3. N-acetylglutamate synthetase deficiency
4. ornithine transcarbamylase deficiency
5. transient hyperammonemia of the newborn

You selected 1, the correct answer is 3.

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In humans, ammonia (NH₄⁺) and aspartate are metabolized to form urea. For each turning of the urea cycle, 1 mol of nitrogen from ammonia and 1 mol of aspartate are incorporated into urea, a water-soluble compound that is excreted in the urine (Figure 1).

Six enzymes catalyze the various steps in this process, each of which has been implicated in clinical disease. Within mitochondria, ammonia derived from serum amino acids, predominantly glutamine and alanine, combines with bicarbonate and adenosine triphosphate in the presence of N-acetyl-glutamate (NAG) and carbamoyl-phosphatase synthetase-1 to form carbamoyl phosphate. The formation of NAG from glutamate and acetyl CoA requires NAG-synthetase, and the reaction to form NAG is normally the rate-limiting step in the overall formation of urea.

Within the mitochondria, ornithine transcarbamylase catalyzes the combination of ornithine with carbamoyl phosphate to form citrulline, which then is transported into the cytosol by a transporter. The second source of nitrogen, aspartate, then combines with citrulline under the effect of arginosuccinate synthetase to form arginosuccinate. Arginine and fumarate formation follow the influence of arginosuccinate lyase and the resulting arginine is converted to urea by the action of arginase-1, resulting in a molecule of ornithine. The ornithine is then transported into the mitochondria to re-enter the cycle by combining with another molecule of carbamoyl phosphate. Citrin (not shown in the Figure) is a carrier protein effecting
the entry of glutamate to and efflux of aspartate from the mitochondria.

Hyperammonemia is the hallmark of the urea cycle defects, occurring in the newborn period with inborn errors affecting all of the urea cycle enzymes other than arginase. Although mild elevations of ammonia normally may be seen in newborns, and infants have higher concentrations than adults, detailed evaluation should be undertaken in any patient with serum ammonia exceeding 140 μg/dL (100 μmol/L).

Ammonia exerts its detrimental effects on the nervous system by at least two mechanisms. By driving the following reaction:

\[\text{Glutamate} + \text{NH}_4^+ \rightleftharpoons \text{Glutamine} + \text{Pi}\]

Hyperammonemia deprives the brain of the glutamate needed to form the neurotransmitter gamma amino butyric acid (GABA). Hyperammonemia may also reverse the following reaction:

\[\text{Glutamate} + \text{NAD}(\text{P})^+ \rightleftharpoons \text{alpha-ketoglutarate}\]

thus depriving the Krebs cycle of one of the components needed for energy metabolism. When hyperammonemia is accompanied by respiratory alkalosis, normoglycemia, and no anion gap, evaluation for a urea cycle defect is indicated.

Defects in the urea cycle occur in approximately 1 in 30,000 live births. The clinical presentation of severe hyperammonemia is common to all but arginase deficiency, but the laboratory profile varies with the specific enzyme involved. Differentiation of the urea cycle defects presenting with severe hyperammonemia can be derived from the following Table.

<table>
<thead>
<tr>
<th>Enzyme deficient</th>
<th>CPS-1 or NAGS</th>
<th>OTC synthetase</th>
<th>ASA lyase</th>
<th>None/Transient Hyperammonemia of Prematurity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical onset (days)</td>
<td>2+</td>
<td>2+</td>
<td>2+</td>
<td>2+ up to 2 weeks</td>
</tr>
<tr>
<td>Sex predilection</td>
<td>M = F</td>
<td>Male</td>
<td>M = F</td>
<td></td>
</tr>
<tr>
<td>Neonatal hyperammonemia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Plasma citrulline</td>
<td>Absent</td>
<td>Absent</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Urine ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine orotic acid</td>
<td>Absent</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASA = arginosuccinic acid; CPS-1 = carbamoyl-phosphatase synthetase-1; NAGS = N-acetyl-glutamate synthetase; OTC = ornithine transcarbamylase; + sign = present; - sign = absent.

The condition most compatible with the options presented in the vignette is NAG-synthetase deficiency. A rare, autosomal recessive form of urea cycle abnormality, this condition presents similarly to carbamoyl-phosphatase synthetase-1 deficiency (also autosomal recessive), with severe hyperammonemia occurring within 2 to 3 days after birth. With the blockage in both of these variants occurring at the entrance to the urea cycle, laboratory studies show no citrulline, low arginine, and elevated glutamine, alanine, and glycine levels. Orotic acid is not elevated. When carbamoyl phosphate is formed and cannot enter the urea cycle, as would be seen in ornithine transcarbamylase deficiency, it is diverted to form orotic acid. Although ornithine transcarbamylase deficiency may present with similarly rapid and severe hyperammonemia as presented in the vignette, it is an X-linked recessive condition, making it unlikely to occur in a female infant. Measurement of plasma citrulline is particularly important, because its presence at normal concentrations in combination with urinary excretion of arginosuccinic acid is...
consistent with ASA lyase deficiency—a condition dramatically improved by treatment with intravenous arginine.

Initial management strategies for acute hyperammonemia that should be begun immediately include:

- Decreasing protein catabolism
  - provide adequate nonprotein calories using glucose and lipids
  - stop exogenous protein input
- Providing nitrogen scavengers
  - intravenous sodium benzoate, which combines with glycine to form hippuric acid, which is excreted in the urine—eliminating 1 molecule of nitrogen per molecule of benzoate
  - sodium phenylacetate (or sodium phenylbutyrate, which is converted to phenylacetate), which condenses with glutamine to form phenylacetylglutamine, also excreted in the urine and eliminating 2 molecules of nitrogen per molecule of phenylacetylglutamine
- priming the urea cycle with arginine, which should be done immediately because it resolves hyperammonemia of ASA lyase deficiency within a few hours, may be helpful in other conditions (not ASA synthetase), and worsens none of the conditions

Severe hyperammonemia in all but ASA lyase deficiency will not respond to medical measures alone, and adequate management usually requires extracorporeal dialysis because exchange transfusion, peritoneal dialysis, and arteriovenous hemofiltration are not as effective. Referral to, or consultation with, a center experienced in the management of acute hyperammonemia should be undertaken promptly.

Arginase deficiency rarely is associated with severe neonatal hyperammonemia. Although the hepatic arginase-1 enzyme may be absent, arginase-2 activity is inducible and is present in many other tissues. Metabolism of the accumulated arginine by these other tissues mitigates the impact of the blockage in the urea cycle. The clinical presentation usually begins subtly in the neonatal period as feeding difficulty, protein intolerance, or somnolence—usually not very severe at first. If unrecognized and untreated, the children progress to have developmental delay, vomiting, protein intolerance, and development of long-tract neurologic impairment often considered to be cerebral palsy. The gene has been mapped to chromosome 6q23. Arginase deficiency is probably the rarest of the urea cycle abnormalities. It is inherited as an autosomal recessive disorder.

Citrin is a carrier protein for the entry of glutamate into the mitochondria and the release of aspartate into the cytosol. Citrin deficiency results in two clinical syndromes, neither presenting with the signs seen in the vignette. The neonatal intrahepatic cholestasis form of citrin deficiency presents at 1 to 4 months of age with direct hyperbilirubinemia, coagulopathy, hypoalbuminemia, mild hyperammonemia, and mildly abnormal liver transaminases. Galactose metabolism may be abnormal, resulting in presence of urinary reducing substances. Patients respond to a lowered protein, galactose-free diet and may need supplementation of fat-soluble vitamins. Hepatic function returns to normal in most patients in the first year, but progression to hepatic failure and liver transplantation has been reported. The adult form presents after age 10 years with hyperammonemia and elevated citrulline concentrations (insufficient aspartate), and often progresses to death resulting from cerebral edema from high ammonia concentrations.

Transient hyperammonemia of the newborn develops mostly in premature infants with onset in the first 24 hours after birth. Although the condition is transient, toxicity from elevated ammonia is a significant risk and aggressive therapy is needed to reduce the ammonia concentration. Secondary hyperammonemia more commonly presents on the first day, and may be associated with organic acid metabolism disorders. Urinary organic acid analysis should be done whenever hyperammonemia is detected in newborns; when absent, search for urea cycle abnormalities should follow. Organic acids are thought to interfere with the activity of NAD-synthetase, resulting in hyperammonemia.

Do you want to add anything to your Learning Plan?
References:


American Board of Pediatrics Content Specification(s):

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle
A pediatric resident asks you to see the 3-month-old sister of a boy who is being followed up in the orthopedic clinic for spastic cerebral palsy and developmental delay. As he was taking the history on the older boy, the mother related that the younger child “is starting to do the same thing.” She relates that both this child and her brother were normal at their term deliveries and both were discharged home before 2 days of age. The young girl is now beginning to have postprandial irritability, episodic vomiting, somnolence, and delayed development in a pattern similar to her older brother. Their 9-year-old brother is healthy, as are the parents.

Of the following, the diagnostic test REQUIRED to confirm the diagnosis in these children involves testing of:

- chromosomes
- erythrocytes
- mitochondria
- serum
- urine

You selected 2, the correct answer is 2.

The children described in this vignette have arginase deficiency, the most infrequently diagnosed of the urea cycle defects. The definitive diagnosis is made with an assay of erythrocytic arginase type 1.

The Figure illustrates the reactions of the urea cycle. Abnormalities of all six of the enzymes have been described, but their clinical presentations vary. With the exception of ornithine transcarbamylase deficiency, which is X-linked recessive in most cases, the defects are autosomal recessive.
Arginase deficiency rarely presents in the neonatal period. Although the blockage in the reaction from arginine to ornithine and urea is completely blocked in the liver, because hepatic arginase type 1 is the deficient enzyme, the water-soluble arginine transfers to other tissues, many of which have inducible arginase type 2 enzyme. For this reason, symptoms in the neonatal period, if any at all, are mild and usually missed. As noted in this vignette, symptoms begin with episodic vomiting, irritability (especially postprandial), lethargy, and somnolence, with progression to developmental retardation and spastic quadriplegia.

Ammonia concentrations may be elevated, but variably so, usually between 140 and 426 μg/dL (100-300 μmol/L), but acute neonatal hyperammonemic events are rarely experienced. Laboratory examinations may reveal elevated serum arginine concentrations, but self-restriction of protein intake makes this an unreliable test. Urinary excretion of arginine will be somewhat increased, but not massively so because of the action of arginase type 2 enzyme. Competitive inhibition of tubular resorption of other amino acids (eg, ornithine, lysine, or cystine) by arginine may give a urinary excretion pattern similar to cystinuria. As arginase is found in the cytosol, mitochondrial analysis would not be helpful. Diagnosis should be confirmed using an arginase type 1 assay on samples of liver biopsy, leukocytes, or erythrocytes, the most convenient tissue to sample.

The disease results from mutations in the gene for arginase type 1 (ARG1), found on chromosome 6q23. In families with known mutations or polymorphisms at the ARG1 locus (not available for the children in the vignette), diagnosis can be confirmed using molecular genetic techniques; prenatal diagnosis can be made based on chorionic villus sampling. Prenatal diagnosis with an enzyme assay requires fetal blood or fetal liver biopsy specimens; the enzyme is not active in cultures of fibroblasts.

Arginine concentrations are being evaluated in newborn screening programs in some states using tandem mass spectrometry. Individuals detected early have responded favorably with normal growth and development to a program of careful monitoring of protein intake, augmented with added sodium benzoate or sodium phenylbutyrate, and supplementation of ornithine and lysine. Careful monitoring is required, and patients should be referred to centers experienced in the management of this condition.

Defects in the other urea cycle enzymes commonly produce acute neonatal hyperammonemic coma after the second day after birth, but arginosuccinic aciduria (deficiency of arginosuccinate lyase) may present as late as 1 to 2 weeks of age. The most common is ornithine transcarbamylase deficiency, the X-linked variant of urea cycle abnormalities. Diagnostic testing using either enzyme assay or molecular genetic techniques is available for each condition.
Citrin deficiency has been related to the urea cycle enzyme defects, because its role is to transport glutamate into the mitochondrion in exchange for the excretion of aspartate from the mitochondrion. The resultant depletion of aspartate in the cytosol causes substrate inhibition of arginosuccinate synthetase, elevated citrulline, and hyperammonemia. Clinical disease is different from the other conditions. The neonatal form presents as intrahepatic cholestasis at 1 to 4 months of age, which often resolves, but can re-emerge as the adult form in later life; the adult form presents after 10 years of age with hyperammonemic citrullemia. Death from hyperammonemic cerebral edema often follows.

References:


American Board of Pediatrics Content Specification(s):

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle

Plan the evaluation of an infant or young child diagnosed with cerebral palsy

Recognize the disorders associated with cerebral palsy, including cognitive and communication disorders, seizures, sensory impairments, orthopedic deformities, emotional, and behavioral disorders

Know the chromosomal disorders and syndromes associated with mental retardation
December: Question 6

A 30-week-gestation premature infant is born after induction for maternal preeclampsia. The birthweight is 1,480 g, and Apgar scores are 7 and 8 at 1 and 5 minutes, respectively. A cord blood sample obtained for blood gases also revealed a calcium concentration of 9.1 mg/dL (2.3 mmol/L). The infant received peripheral alimentation initially, but quickly tolerated feedings of breast milk per gavage. Serum calcium concentration, repeated at the beginning of the third day, was 7.4 mg/dL (1.8 mmol/L). The calcium concentration was followed, and no specific treatment was initiated because there were no symptoms of hypocalcemia. By the 10th day, when the infant was receiving full feedings, the serum calcium concentration was 10 mg/dL (2.5 mmol/L).

Of the following, the factor MOST responsible for the transient fall and then rise of serum calcium concentration in this infant is:

1. calcitonin
2. calcitrol (1,25 dihydroxy vitamin D3)
3. gastrointestinal absorption
4. parathyroid hormone
5. renal tubular maturation

You selected 3, the correct answer is 3.

The hormonal regulators of serum calcium concentration include parathyroid hormone, vitamin D, and calcitonin. Parathyroid hormone is a peptide produced by the parathyroid glands in response to low ionized calcium. Receptors sensitive to the extracellular fluid calcium concentration are present in the parathyroid gland and in the kidneys. Parathyroid hormone increases serum calcium concentration through four separate mechanisms:

- stimulates reabsorption of calcium from bone
- increases urinary excretion of phosphorus
- decreases urinary excretion of calcium
- increases renal synthesis of 1,25 dihydroxy vitamin D (calcitrol)

Serum calcium concentrations have been measured in a series of premature infants in the first several days after birth as shown in the Figure.

Figure: Serum calcium concentration (mg/dL) in premature infants. (From Rigo and De Curtis [2006]).
The concentration is highest at 10 days after which calcium concentration levels off. The mean concentration in cord blood is typically 90% of the concentration found at 10 days of age. After the birth of a premature infant, the serum concentration of calcium falls to a nadir around 48 hours (around 75% of the subsequent steady state value). A transient fall in serum calcium concentration is also seen in normal term infants but it is less dramatic and does not last as long. Stressed infants, such as those of diabetic mothers and those with birth asphyxia, can have an exaggerated and prolonged depression of the serum calcium concentration.

These transient episodes of hypocalcemia that begin just after birth have been attributed to a delayed response of the parathyroid glands in the production and/or release of parathyroid hormone to falling calcium concentrations. The fetus receives a continuous transplacental calcium infusion throughout gestation via active transport. About 28 g of calcium is accumulated over 40 weeks, two thirds of which is transferred during the last trimester. The placenta transfers as much as 120 to 150 mg of calcium per kilogram of fetal weight per day. Fetal serum concentrations exceed maternal values and functionally suppress fetal parathyroid hormone production. Parathyroid hormone does not cross the placenta. The main regulator of the maternal-fetal calcium gradient is thought to be parathormone-releasing protein and not parathyroid hormone. Parathormone-releasing protein is produced by the placenta as well as the fetal parathyroid gland and other fetal tissues.

At birth, when the continuous supply of calcium from the maternal circulation ceases, the calcium concentration begins to fall. This stimulates both the rapid secretion of parathyroid hormone already produced and the production of new parathyroid hormone. The initial response occurs within seconds, but because the parathyroid glands were suppressed before birth, the initial concentration of the hormone is low and less hormone is available for immediate secretion. The production of new hormone is not instantaneous, because it depends on messenger RNA production and, over time, the growth of the parathyroid glands. It generally takes 2 days in a premature infant to achieve peak concentrations (1 day in a full-term infant and a variable time in stressed infants). In each case, the timing of the change in parathyroid hormone concentration corresponds with the course of the transient hypocalcemia.

Calcitonin is also a peptide hormone. It is produced by the parafollicular cells of the thyroid gland. It is a physiologic antagonist to parathyroid hormone and reduces serum calcium by inhibiting the activity of osteoclasts, slowing bone resorption. It can also increase renal excretion of calcium and phosphorus. Calcitonin concentration at birth is higher than that of the pregnant mother, rises to a peak at 24 to 48 hours of age, and then gradually declines to childhood concentrations during the next month. This pattern does not correspond to the timing
of transient hypocalcemia seen in newborn infants.

Calcitrol (1,25 dihydroxy vitamin D3) can be produced in the skin with the aid of ultraviolet light (ergo, not in utero), or via ingestion and absorption of the vitamin. Hydroxylation occurs in two steps. The liver produces the first hydroxylation (at the 25 position) and the proximal renal tubules produce the second. The renal tubule responds to hypocalcemia, hypophosphatemia, and parathyroid hormone by increasing the rate of 1-hydroxylation. The vitamin is then transported through the circulation to the small intestine where it enhances calcium and phosphorus absorption, and to bones where it assists in calcium resorption. Calcitrol is transported by the placenta, and the initial neonatal concentration reflects the maternal concentration. In preterm infants, calcitrol concentrations at birth are similar to those of adults and are even higher in the first 3 months.

Renal tubular mechanisms that respond to parathyroid hormone and synthesize calcitrol do not exhibit adaptive development during the period typical of transient hypocalcemia. Furthermore, the gastrointestinal functions related to calcium absorption do not contribute to transient hypocalcemia. In both cases, responsiveness to parathyroid hormone and calcitrol is similar to that seen later in life.

References:


American Board of Pediatrics Content Specification(s):

Understand the interrelated effects of various hormones, including parathormone, calcitonin, and vitamin D on calcium, phosphorus, and magnesium metabolism in the fetus and neonate.
For the infant younger than 12 months of age, differences in nutritional composition make bovine (cow) milk a poor substitute for human milk. Commercially available formulas designed to mimic the composition of human milk provide a better alternative when human milk is unavailable.

Of the following, the constituent found in HIGHER concentrations in whole bovine milk than in mature human milk is:

1. carbohydrate
2. fat
3. folic acid
4. protein
5. vitamin E

You selected 1, the correct answer is 1.

Do you want to add anything to your Learning Plan?
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Multiple differences exist between the nutritional composition of cow's milk (CM) and human milk (HM) (Table). Most of these differences put CM at a disadvantage and make it an undesirable substitute for HM in the neonate.

Table
The protein concentration of whole CM is nearly four times that of mature HM (3.3 g/100 mL versus 0.9 g/100 mL). Qualitative differences in protein composition exist as well. For both HM and CM, protein constituents can be classified as either casein or whey. Caseins are proteins with low solubility in acid media. Whey proteins promote more rapid gastric emptying, and remain in solution after acid precipitation, facilitating their digestion. Mature HM is predominantly whey, with a whey-to-casein ratio of 60:40. Conversely, the fraction of whey in whole CM is relatively small (whey-to-casein ratio of 18:82).

In addition, HM and CM differ in the types of protein contained in the whey fraction. In HM, the major whey protein is α-lactalbumin, while the major whey protein in CM is β-lactoglobulin. Additional whey proteins found in high quantities in HM and involved in host defense include lactoferrin, lysozyme, and secretory immunoglobulin A. These proteins are present only in trace quantities in CM.

The carbohydrate concentration of whole CM is less than that of mature HM (4.8 g/100 mL versus 6.7 g/100 mL). Both CM and HM contain lactose, which promotes softer stool, more nonpathogenic bacterial fecal flora, and improved absorption of minerals attributed to the presence of small quantities of unabsorbed lactose. Oligosaccharides, present in HM, play a role in host defense, because their structure mimics specific bacterial antigen ligands and prevent bacterial attachment to host mucosa.

The lipid concentration of whole CM is also less than that of mature HM (3.4 g/100 mL versus 3.9 g/100 mL). In HM, the lipid system provides 50% of the calories of the milk, and is structured to promote fat digestion and absorption. Lipids in HM are organized as fat globules and are higher in long-chain fatty acids than CM (98% versus 92%). Linoleic and linolenic acid (essential fatty acids) are found in limited amounts in CM. Likewise, arachidonic and docosahexaenoic acids (derivatives of linoleic and linolenic acids) are found in HM but not CM. These very-long-chain polyunsaturated fatty acids are important constituents of brain phospholipid membranes and have been linked to improved neurodevelopmental outcome. In addition, HM contains bile salt–stimulated lipase that facilitates fat digestion, resulting in less fat in the stool.

### Table. Composition of Cow's Milk and Human Milk

<table>
<thead>
<tr>
<th>Component</th>
<th>Whole Cow's Milk</th>
<th>Mature Human Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, g/100 mL</td>
<td>3.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Whey/casein ratio, %</td>
<td>18:82</td>
<td>60:40</td>
</tr>
<tr>
<td>Fat, g/100 mL</td>
<td>3.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Carbohydrate, g/100 mL</td>
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<tr>
<td>Major minerals, mg/100 mL</td>
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</tr>
<tr>
<td>Sodium</td>
<td>50</td>
<td>12.25</td>
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<tr>
<td>Potassium</td>
<td>156</td>
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</tr>
<tr>
<td>Chloride</td>
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<td>42</td>
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<tr>
<td>Calcium</td>
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<tr>
<td>Phosphorus</td>
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<td>12.14</td>
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<tr>
<td>Magnesium</td>
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<tr>
<td>Trace minerals, µg/L</td>
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</tr>
<tr>
<td>Iron</td>
<td>460</td>
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<tr>
<td>Zinc</td>
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<tr>
<td>Copper</td>
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<tr>
<td>Water-soluble vitamins</td>
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<tr>
<td>Ascorbic acid, mg/L</td>
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<tr>
<td>Folic acid, µg/L</td>
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<td>Pyridoxine, µg/L</td>
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<tr>
<td>Vitamin K, µg/L</td>
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</tr>
</tbody>
</table>

The carbohydrate concentration of whole CM is less than that of mature HM (4.8 g/100 mL versus 6.7 g/100 mL). Both CM and HM contain lactose, which promotes softer stool, more nonpathogenic bacterial fecal flora, and improved absorption of minerals attributed to the presence of small quantities of unabsorbed lactose. Oligosaccharides, present in HM, play a role in host defense, because their structure mimics specific bacterial antigen ligands and prevents bacterial attachment to host mucosa.

The lipid concentration of whole CM is also less than that of mature HM (3.4 g/100 mL versus 3.9 g/100 mL). In HM, the lipid system provides 50% of the calories of the milk, and is structured to promote fat digestion and absorption. Lipids in HM are organized as fat globules and are higher in long-chain fatty acids than CM (98% versus 92%). Linoleic and linolenic acid (essential fatty acids) are found in limited amounts in CM. Likewise, arachidonic and docosahexaenoic acids (derivatives of linoleic and linolenic acids) are found in HM but not CM. These very-long-chain polyunsaturated fatty acids are important constituents of brain phospholipid membranes and have been linked to improved neurodevelopmental outcome. In addition, HM contains bile salt–stimulated lipase that facilitates fat digestion, resulting in less fat in the stool.
Human milk and CM also differ with respect to the concentrations of vitamins and major and trace minerals. In general, concentrations of each are higher in CM. Notable exceptions (higher concentrations in HM than in CM) include folic acid, vitamin E, vitamin A, ascorbic acid, niacin, and copper. Substantially higher concentrations of sodium, potassium, and chloride in CM than in HM, coupled with the higher protein concentration, raise the renal solute load in infants consuming CM by as much as twofold, predisposing the infant to dehydration. Although the bioavailability of iron in HM is better, CM and HM are both poor sources of iron, and iron supplementation is recommended to prevent iron-deficiency anemia.

References:


American Board of Pediatrics Content Specification(s):

Understand the differences in the nutritional composition of human milk and cow milk
A male infant is born at 36 weeks' gestation to a mother with Graves disease. The newborn state screen shows that the infant has elevated thyroid-stimulating hormone and thyroxine concentrations. This corresponds with the excessive thyroid-stimulating hormone receptor-stimulating antibodies measured in the infant's mother.

Of the following, the MOST likely mechanism for transplacental transfer of these antibodies is:

1. active transport
2. facilitated diffusion
3. pinocytosis
4. placental break
5. simple diffusion

You selected 3, the correct answer is 3.

The infant in this vignette developed hyperthyroidism because of the intrauterine transplacental passage of the maternal thyroid-stimulating hormone receptor immunoglobulin (Ig) G antibodies. Pinocytosis is the process enabling IgG molecules to cross the placenta. During this process, trophoblasts on the maternal side of the placenta bind and engulf IgG molecules via specific neonatal Fc receptors, transport them across the cell, and release the antibodies on the fetal side. Because these Fc trophoblastic receptors bind specifically to IgG, this is the only major class of antibodies that can cross the placenta. Transplacental passage of IgG molecules increases with advancing gestational age, beginning early in the second trimester with most of the antibodies being transferred during the third trimester. Antibody transfer enables newborns to have a passive defense mechanism against some pathogens (a positive effect), or antibody transfer might cause transient manifestations of maternal antibody-mediated disease, such as Graves disease, myasthenia gravis, or autoimmune thrombocytopenia purpura (a negative effect).

Active transport is the carrier-mediated transfer of compounds against the concentration gradient that requires the expenditure of energy. Because the concentrations of amino acids, calcium, phosphate, magnesium, and water-soluble vitamins in fetal blood are greater than in maternal blood concentrations, these substances are transferred from the maternal to the fetal side of the placenta with this mechanism. Amino acids are actively transported into the syncytiotrophoblast via specific transporters and are then transferred by a passive leak down the concentration gradient to the fetal plasma. At least 10 sodium-dependent amino acid transporters have been identified in the placenta. Active transport mechanisms for amino acid placental transfer are intact by the late second trimester because fetal amino acid concentrations are higher than maternal concentrations by 18 to 21 weeks'
Placental facilitated diffusion is the energy-independent movement of molecules across the microvillous or basal membranes of the syncytiotrophoblasts using transport proteins. This passive transfer is mediated by carrier proteins and occurs along the concentration gradient. Glucose is transported across the placenta by insulin-independent facilitated glucose transporters, also known as GLUT transporters. GLUT 1 is the most abundant subtype expressed in the human trophoblast.

Breaks in the placental membrane are caused by abnormalities within the placental structure and can cause maternal or fetal cells to cross the placenta. These breaks are atypical and are not involved in the normal transfer of compounds across the placenta.

Simple diffusion is the passive transfer of solutes. Oxygen, carbon dioxide, water, sodium, chloride, lipids, fat-soluble vitamins, and most maternal medications are transferred across the placenta with this mechanism. The direction of transplacental passage of these molecules depends on the: (1) concentration gradient; (2) surface area of the placental membrane; (3) placental blood flow; and (4) properties of the compounds, including lipid solubility, molecular weight, and protein-binding.

References:


Simister NE. Placental transport of immunoglobulin G. *Vaccine*. 2003;21(24):3365-3369

American Board of Pediatrics Content Specification(s):

Understand the placental transfer of immunoglobulins

Know the role of the placenta in the energy metabolism of the fetus, including transfer of glucose, electrolytes, and amino acids to the fetus
A term newborn infant develops hypoglycemia unresponsive to feeding in the first hours after birth. The blood glucose concentration is 21 mg/dL (1 mmol/L) and 36 mg/dL (2 mmol/L) before and after feeding, respectively. Physical examination shows an infant with normal growth. The external genitalia consist of a small phallus and a rugated scrotumlike sac containing gonads. The gonads measure 1 cm in the long axis. The stretched phallus measures 1.9 cm in length and 0.7 cm in diameter. The rest of the physical examination findings are normal. The newborn’s blood glucose concentration improves with an intravenous glucose infusion, but gradual weaning is unsuccessful during the next several days.

Of the following, the most likely diagnosis for the infant in the vignette is:

1. aromatase deficiency
2. chromosome abnormality (47,XXY)
3. congenital adrenal hyperplasia
4. isolated cortisol deficiency
5. pituitary insufficiency

You selected 5, the correct answer is 5.

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The infant in the vignette almost certainly has pituitary insufficiency which affects both glucose homeostasis and genital development. The persistent requirement for higher than normal glucose intake to maintain normal blood glucose concentrations is because of a lack of pituitary hormone production (eg, growth hormone and adrenocorticotropic hormone [ACTH]) that would oppose the effects of insulin and increase glucose production. Growth hormone (somatotropin) and adrenal glucocorticoids (eg, cortisol) promote gluconeogenesis and help raise blood glucose concentrations. Growth hormone also suppresses the uptake of glucose by the liver. With pituitary insufficiency, growth hormone and ACTH are not secreted, resulting in hypoglycemia from unopposed insulin action.

The normal size of the stretched penis at birth is 2.5 to 5 cm with a diameter of 0.9 to 1.3 cm. The infant in this vignette has a micropenis (http://knowledge.emedicine.com/splash/shared/pub/cotw/0028answer.html). The testes in a newborn are normally 8 to 14 mm long. Penile development depends on the normal production of testosterone which is stimulated by pituitary-derived luteinizing hormone (LH). The production of adrenal androgens is stimulated by ACTH which is also deficient in this condition. An isolated deficiency of growth hormone, which occurs far less commonly than panhypopituitarism, could also present with hypoglycemia and micropenis. Isolated growth hormone deficiency was not an option offered in the vignette.

Aromatase (also known as cytochrome P450 aromatase) is a microsomal enzyme complex that converts androgenic steroids to estrogens.
Aromatase deficiency is a rare disease caused by a mutation of gene CYP19 on chromosome 15 (15q21.2). It is an autosomal recessive disorder. Accumulation of androgens during pregnancy may cause virilization of a newborn female. Males are not affected. Females will have primary amenorrhea. Individuals of both sexes will be tall because the epiphyses remain open as a result of a lack of estrogen. Neonatal hypoglycemia is not described in this disorder.

The chromosome abnormality 47,XXY is also known as Klinefelter syndrome. Boys with Klinefelter syndrome inherit an extra X chromosome from either mother or father owing to nondisjunction during meiosis. Klinefelter syndrome occurs in 1 in 500 to 1 in 1,000 male births. The testes are small and firm. Other effects of Klinefelter syndrome are quite variable. Boys with Klinefelter syndrome are usually born with external genitals that look like those of other boys; however, micropenis at birth is described in some cases. Neonatal hypoglycemia is not a feature of Klinefelter syndrome.

Congenital adrenal hyperplasia (CAH) in girls presents with virilization including an enlarged clitoris that might be confused with a micropenis and rugated labia majora that can be confused with a bifid scrotal sac. However, finding gonads in these skin folds is highly unusual in girls with CAH. Boys with CAH have a normal appearance at birth, including that of their external genitalia. The prevalence of some degree of enzyme deficiency leading to variations in this condition is 1 in 60 individuals in the general population. Neonatal hypoglycemia can occur with CAH, but is not a common presentation.

Familial isolated glucocorticoid deficiency is a rare autosomal recessive disorder that presents as primary adrenal insufficiency, usually without mineralocorticoid deficiency, that can be lethal, if unsuspected. Indeed, in more than 50 published cases, 18 have been fatal. Affected children can present within the first 2 to 3 years of age with hyperpigmentation and recurrent hypoglycemia that can lead to convulsions or coma, chronic weakness, and failure to thrive. Typically they have deficient production of cortisol and adrenal androgens, in the presence of markedly elevated ACTH concentrations. Affected subjects achieve normal growth and development with steroid replacement and live an otherwise normal life. Testosterone production is not affected and micropenis is not described.

Do you want to add anything to your Learning Plan?
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References:


American Board of Pediatrics Content Specification(s):

Know the importance of the combination of micropenis and hypoglycemia
You are asked to review a chest radiograph of an infant being seen by his pediatrician. The 4,193-g boy was delivered last evening by scheduled, repeat cesarean section at 39 weeks’ gestation to a 29-year-old mother. He had received oxygen overnight, but now is in room air with a respiratory rate of 70 breaths per minute. The chest radiograph was just taken (Figure).

Of the following, the cardiac finding on the chest radiograph is MOST likely the result of:

1. alpha-iduronidase deficiency
2. carnitine deficiency
3. hyperinsulinism
4. lysosomal alpha-1,4-glucosidase deficiency
5. viral cardiomyopathy

You selected 3, the correct answer is 3.

Hyperinsulinism resulting from maternal hyperglycemia is the most likely underlying cause for this infant's pronounced cardiomegaly. Often mothers with gestational diabetes go undetected in spite of their insulin intolerance and hyperglycemia during pregnancy. Fetal insulin concentrations increase in response to the glucose transferred across the placenta, resulting in fetal macrosomia, hypertrophic cardiomyopathy, and organomegaly involving the liver and muscles.

Despite improving respiratory status, which was likely a result of delayed fluid mobilization from the lung secondary to cesarean delivery without preceding labor, and no apparent signs of deterioration, the infant should be carefully observed. Many of these infants will have a systolic outflow murmur associated with septal hypertrophy, and some will have significant cardiac...
obstruction. An echocardiogram may be helpful.

L-Carnitine (β-hydroxy-β-trimethylaminobutyric acid) is an essential component in the transport of long chain fatty acids into mitochondria, where they undergo β-oxidation. Low concentrations of carnitine are common in premature infants receiving total parenteral nutrition without adequate carnitine supplementation. Because the normal heart receives approximately 60% of its total energy supply from fatty acid oxidation, this function of carnitine is thought to be of major importance. A number of case reports have shown that some patients with carnitine deficiency will exhibit cardiomyopathy. Adequate concentrations of carnitine are required for normal energy metabolism and contractile function of the heart. Although short-term moderate secondary carnitine deficiency, in and of itself, does not have a major effect on the cardiac contractile function, substrate oxidation may be altered. With longer durations of carnitine deficiency, alterations occur within the heart that may result in impaired contractile performance. These patients generally present with additional metabolic derangements including profound hypoglycemia. In this vignette, carnitine deficiency is unlikely to be the cause of cardiomegaly.

Some viruses including the coxsackie B virus may cause severe and often fatal infections in newborn infants. Infection may be transmitted transplacentally in late pregnancy, with the infant developing heart failure after delivery, because of severe myocarditis. More frequently, infection is transmitted during the birth process or postnatally via the mother or other virus-infected infants in the hospital. Some infected neonates may be asymptomatic, but others may develop illness at 3 to 7 days after exposure ranging from a mild febrile illness to a severe fulminant multisystem disease and death. Myocarditis, pneumonia, and meningoencephalitis may occur in addition to severe hepatitis that may be accompanied by profuse hemorrhage. Coxsackie B virus can be recovered from the myocardium, brain, spinal cord, and feces. In this vignette, the infant is well appearing without systemic illness; thus, the cardiomegaly is unlikely to be secondary to a viral infection.

Hurler disease is a mucopolysaccharidosis caused by a defect in alpha-iduronidase. Infants with this disease present later than seen in this vignette. Affected patients usually present closer to 1 year of age with cloudy corneas, hepatosplenomegaly, coarse facial features, hirsutism, stiff joints, kyphosis, and poor central nervous system function.

Pompe disease is an autosomal recessive disorder caused by mutations in the gene encoding lysosomal alpha-1,4-glucosidase. The classic infantile form of this disorder is characterized by cardiomyopathy and severe generalized muscular hypotonia. The median age at symptom onset is reported to be 2 months and at diagnosis 5 months. Presenting findings include cardiomegaly (92% of infants), respiratory distress (78%), muscle weakness (63%), feeding difficulties (57%), and failure to thrive (53%). Pompe disease would be unlikely to produce pronounced cardiomegaly within 5 days of birth.

References:

Breningstall GN. Carnitine deficiency syndromes. Ped Neurol. 1990;6:75-81


van den, Hout HM, Hop W, van Diggelen OP, et al. The natural course of infantile Pompe's
disease: 20 original cases compared with 133 cases from the literature. *Pediatrics*. 2003;112:332


**American Board of Pediatrics Content Specification(s):**

Understand the pathophysiology, including genetics, of an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Recognize the clinical features in an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Recognize the laboratory and radiographic features of an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Formulate a differential diagnosis of an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Know the normal range of endogenous glucose production in term and preterm infants

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids

Understand the clinical manifestations, diagnostic criteria, and treatment of perinatal infections with coxsackievirus, echovirus, enterovirus, and poliovirus

Understand the etiology, clinical manifestations, laboratory features, treatment, and management of infants with lysosomal and peroxisomal, and mitochondrial disorders
You are called to the emergency room for a primagravida mother delivering precipitously at 30 weeks’ gestation. You arrive before the obstetrician. The soon-to-be father tells you that the mother takes a medicine for some sort of a thyroid problem. As you prepare for the birth of the infant, you consider the potential fetal and neonatal complications that may accompany maternal thyroid disorders and treatments.

Of the following, the substance that BEST crosses the placenta is:

1. iodide ion
2. thyroid-stimulating hormone
3. thyrotropin-releasing hormone
4. thyroxine
5. triiodothyronine

You selected 1, the correct answer is 1.

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The thyroid hormones contribute relatively little to growth of the fetus compared with that of the child. Fetal growth is most dependent on insulin and insulin-like growth factors, while childhood growth is dependent on both thyroid and growth hormones. In general, the maternal and the fetal thyroid systems remain separate and largely independent. However, there is some interaction between maternal and fetal thyroid physiologic processes, with the fetus needing either a normal endogenous thyroid system, or a mother with a normal thyroid system for growth and development. If both maternal and fetal systems are deficient, as with an athyrotic infant born to an untreated hypothyroid mother, the child is at risk for developmental delays.

During fetal life, some substances involved in the normal thyroid system can cross the placenta. The mother is the sole source of fetal iodide ion, which passes freely across the placenta to the fetus. Thyrotropin-releasing hormone (TRH), made by the fetus or the mother, can cross the placenta to some degree. Thyroxine (T4) and triiodothyronine (T3) can cross the placenta in small amounts only. Thyroid-stimulating hormone (TSH) does not cross the placenta.

Iodide ion crosses the placenta with the aid of several membrane transport proteins, including pendrin, a protein also found in the thyroid gland. Iodide is essential for the production of T3 and T4. Although T3 and T4 concentrations in the first trimester fetus are almost undetectable, the absence of iodide ion at this time is associated with developmental deficiencies. The World Health Organization has stated that dietary iodine deficiency is the world’s leading cause of preventable mental retardation. Iodide deficiency can sometimes manifest as fetal goiter, because of the overabundance of fetal TSH made in response to the abnormally low T3 and T4 concentrations. Interestingly, too much iodide ion can also cause fetal goiter, by inhibiting release of T4 and T3 from the thyroid gland, again causing an overabundance of TSH.
Thyroid-stimulating hormone also known as thyrotropin, is a 16-kD glycoprotein similar in structure to human chorionic gonadotropin. It is made in the anterior hypophysis in response to TRH or in response to low T3 and T4 concentrations. It does not cross the placenta. The concentration of TSH in the fetus may be as much as twofold higher than that in the mother.

Thyrotropin-releasing hormone is a tripeptide made in the hypothalamus and transported to the anterior pituitary via the hypophyseal portal venous system. Fetal TRH is made in the pancreas and in the placenta, as well as in the hypothalamus. A TRH-degrading enzyme in the maternal blood limits maternal serum TRH to nearly immeasurable concentrations, so very little ever reaches the placenta. Exogenously administered TRH can cross the placenta to some degree, and has been studied as an agent to enhance fetal lung maturation, with inconsistent results.

Thyroxine, also known as tetraiodothyronine, is found in species ranging from tunicates to frogs, where it is involved in the metamorphosis from tadpole to adult. In humans, T4 elevates cellular metabolism by binding to proteins in the nuclei of certain cells to modulate transcription of certain genes. Its synthesis is based on two tyrosine residues, each with two iodine molecules. Only small amounts of T4 are made in the fetus, and even smaller amounts are transmitted from the mother to the fetus. The fetal serum concentration of T4 in midgestation is around 1% of the maternal serum concentration. These small amounts may have some significance for the fetus. Because of a relatively low concentration of thyroid-binding globulin in the fetus, more of the fetal T4 is in the active free-T4 state rather than the inactive, bound state.

Triiodothyronine is structurally similar to T4, but missing an iodine in the outer ring. It is 6 to 10 times more potent than T4, but is made by the thyroid gland at half the rate of T4. Peripheral conversion in certain tissues of T4 to T3 is the largest source of T3. The T4-to-T3 converting enzyme is present earliest and in highest concentration in the fetal brain, suggesting the importance of the thyroid system to fetal brain development. Only a small amount of maternal T3 crosses the placenta.

References:


American Board of Pediatrics Content Specification(s):

Understand the relationship between fetal and maternal thyroid physiology

Know the physiological roles of the hormones and other proteins involved in the regulation of thyroid function
A primagravida is referred to you by a perinatologist to discuss the potential effect of her hypothyroidism on the child. Review of her history indicates early-onset hypothyroidism associated with an ectopic, hypoplastic thyroid. She has required supplementation with thyroid hormone. She is a prominent fish merchant, and has heard that the fetal thyroid gland comes from fishlike gills in the embryo. She asks you about this relationship and wants to understand the formation of the thyroid gland.

Of the following, the MOST important precursor to the isthmus of the thyroid gland is the:

1. fifth pharyngeal pouch
2. fourth pharyngeal pouch
3. pharyngeal floor
4. Rathke's pouch
5. third pharyngeal pouch

You selected 3, the correct answer is 3.

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The thyroid gland comprises several tissues and structures, including the thyroid hormone-secreting follicular cells, the calcitonin-secreting parafollicular C cells, and the four parathyroid glands. These tissues derive from several anlagen (Figure). The bulk of the tissues of the thyroid gland originate in the pharyngeal floor and the fourth pharyngeal pouch, and that portion that forms the isthmus is mainly derived from the pharyngeal floor.

Figure: Posterior view of the thyroid gland tissues and their origins
The gills that are vital for fish and larval amphibians are not needed by air-breathing mammals. When the gills (Greek: *branchia*) form in the mammalian embryo, their structure becomes available for the development of the branchial apparatus. Evolution has played freely with this apparatus, so that the originally simple gill-like structures undergo extensive migration and differentiation in the mammalian embryo before settling on their final function in their final site.

The embryo forms four main branchial arches, as well as two more rudimentary arches, anterior and lateral to the pharynx. The pharynx bulges out between these arches to form four main pharyngeal pouches and a rudimentary fifth. Students often ask how a space, or pouch, can later form a structure; they can be guided by the concept of the resulting structures being formed by the cells lining the pouch, multiplying, and eventually filling in the migrating potential spaces.

The greatest portion of the thyroid gland begins on the pharyngeal floor. It migrates from an area that becomes the posterior aspect of the tongue, leaving a small remnant pit at the base of the tongue called the foramen cecum. The migration of the thyroid diverticulum proceeds caudally along the thyroglossal duct until it reaches the level of the fourth branchial arch. This migration is thought to be linked to the migration of the anlagen of the heart and thymus caudally into the thorax. The midline portion of the thyroid then spreads laterally, and fuses with tissues derived from the fourth branchial pouch, to form the complete thyroid gland by day 50 of gestation. Rarely, remnants of the thyroglossal duct may form midline cysts or sinuses.

The third pharyngeal pouch produces the inferior parathyroid glands, and the fourth pharyngeal pouch produces the superior parathyroid glands. The parathyroid glands migrate with the thyroid anlage and remain on the thyroid's posterior aspect.

The fifth pharyngeal pouch is an ill-defined area incorporated into the caudal end of the fourth pharyngeal pouch to form the ultimobranchial body. This body fuses with the thyroid gland and disperses to form the parafollicular C cells. Although these cells secrete calcitonin, they are labeled “C” because they appear clear on hemotoxylin-eosin staining.

Rathke's pouch is an invagination of the pharyngeal roof. Made of oral ectoderm, it extends toward the neuroectoderm of the infundibulum to form the anterior pituitary gland, which will eventually produce thyroid-stimulating hormone. It was named after Martin Heinrich Rathke, an amiable 18th-century German anatomist known for his important work on the comparative anatomy of the embryonic branchial apparatus.

To specifically answer the mother's concern in the vignette: because her hypothyroidism does not involve antithyroid antibodies that cross the placenta, and her hypothyroidism is adequately treated, the likelihood that the pregnancy will be affected is low. The infant likely will not have thyroid problems, and informing her about neonatal screening can reassure her concerns about
her child's development.

Do you want to add anything to your Learning Plan?
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References:


American Board of Pediatrics Content Specification(s):

Understand the embryology and normal physiological function of the normal thyroid gland

Know the physiological roles of the hormones and other proteins involved in the regulation of thyroid function
May: Question 4

A 34-year-old primiparous woman is carrying a fetus at an estimated gestational age of 28 weeks. Her history is significant for hypothyroidism secondary to autoimmune thyroiditis diagnosed 4 years earlier for which she is receiving thyroid hormone treatment. She inquires whether the thyroid hormone can cross the placenta and affect the thyroid function of her fetus.

Of the following, the hormone MOST readily transferred across the placenta is:

1. reverse triiodothyronine
2. tetraiodothyronine
3. thyroid-stimulating hormone
4. thyrotropin-releasing hormone
5. triiodothyronine

You selected 5, the correct answer is 5.

Do you want to add anything to your Learning Plan?
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All forms of thyroid disease are more common in women than in men, and hypothyroidism is not a rare event during pregnancy, occurring in about 2 cases per 1,000 pregnancies. Autoimmune thyroiditis is the most common cause of hypothyroidism among pregnant women. Thyroid microsomal and peroxidase antibodies are positive in 60% to 90% of such cases. These antibodies readily cross the placenta and may cause transient neonatal hypothyroidism by blocking thyroid function.

To understand the placental permeability of hormones related to thyroid function, it is important to examine the hypothalamic-pituitary-thyroid (HPT) axis of thyroid hormone regulation as well as the synthesis of the thyroid hormones. The HPT axis (Figure 1) represents the feedback loop of thyroid hormone regulation.

Figure 1: Hypothalamic-pituitary-thyroid axis
Low circulating concentrations of thyroid hormones stimulate the hypothalamus, specifically the paraventricular nucleus, to secrete thyrotropin-releasing hormone (TRH). The TRH stimulates the thyrotropic cells of the anterior pituitary to secrete thyroid-stimulating hormone (TSH), which induces the secretion of thyroid hormones by the thyroid gland. Conversely, excess thyroid hormones in circulation suppress the hypothalamic TRH, which inhibits the pituitary TSH and lessens the stimulatory effect of TSH on the thyroid gland, reducing the circulating concentrations of thyroid hormones. This dynamic balance maintains concentrations of thyroid hormones in the physiologic range.

Thyroid hormone synthesis involves three critical steps:

- uptake of iodide
- iodination of tyrosine
- deiodination of thyronines

Iodine is absorbed in the alimentary tract in the form of iodide, which is taken up avidly by the thyroid gland under the influence of TSH. Iodination of tyrosine involves incorporation of iodine in specific positions within the tyrosyl ring of thyroglobulin, a glycoprotein synthesized by the endoplasmic reticulum of the thyroid follicle cells. This iodination of tyrosine is catalyzed by the enzyme thyroid peroxidase. The resultant iodothyrosines are monoiodothyrosine (3-iodotyrosine) (Figure 2) and diiodothyrosine (3,5-diiodothyrosine) (Figure 3).

Figure 2: Monoiodothyrosine
These iodotyrosines have no hormonal activity. Coupling of the iodotyrosines, under the influence of thyroid peroxidase, results in the formation of iodothyronines. Each iodothyronine has two rings, an inner tyrosyl ring with positions designated as 3 and 5, and an outer phenolic ring with positions designated as 3' and 5'. Tetraiodothyronine (3,3',5,5'-tetraiodothyronine) (thyroxine, T₄) (Figure 4) is the principal product of thyroid hormone synthesis. It has minimal biologic activity and acts mainly as a precursor of active thyroid hormone.

Removal of iodine (deiodination) from specific positions in the tyrosyl and phenolic rings of T₄, under the influence of deiodinase, is required for the formation of functional thyroid hormones outside the thyroid gland. Triiodothyronine (3,3',5-triiodothyronine; T₃) (Figure 5) is derived by 5'-deiodination; it is the most biologically active form of thyroid hormone. Reverse triiodothyronine (3,3',5'-triiodothyronine; rT₃) (Figure 6) is derived by 5-deiodination; it is biologically inactive.
Further deiodination results in the formation of diiodothyronines and monoiodothyronines, which have no biological activity. The process of deiodination of thyronines is critical for balancing thyroid function; 5'-deiodination is predominant when active thyroid hormone is needed, whereas 5-deiodination prevails when thyroid function needs to be suppressed.

Among the hormones related to thyroid function listed in this vignette, TRH has the most placental permeability. Maternal administration of TRH is accompanied by increased concentrations of TSH, T4, and T3 in umbilical cord blood, which indicates stimulation of the fetal thyroid. This action of TRH has raised the possibility for maternal intervention with antenatal TRH treatment, used in conjunction with antenatal glucocorticosteroid treatment, to upregulate fetal thyroid function as a means of accelerating fetal lung maturation. In trials conducted before the advent of postnatal surfactant administration, an antenatal combination treatment with TRH and glucocorticosteroid in mothers with impending preterm deliveries was shown to be beneficial in reducing the risk of neonatal respiratory distress. Subsequent trials, after the establishment of surfactant use, however, have shown that a combination of antenatal glucocorticosteroid and postnatal surfactant treatment is effective in reducing the risk of neonatal respiratory distress, and that this benefit is not enhanced further by the addition of antenatal TRH.

The placenta has limited permeability to thyroid hormones. Large doses of T4 given to the mother produce only minor changes in the concentrations of thyroid hormones in the umbilical cord blood. Much of the placental impermeability is attributed to the presence of 5-deiodinase enzyme in the placenta, which rapidly converts T4, T3, and rT3 into diiodothyronines that have no biologic activity. The placenta is largely impermeable to TSH. The fetus of the woman in this vignette is not likely to be affected by her thyroid hormone treatment during pregnancy.

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References:


**American Board of Pediatrics Content Specification(s):**

Understand the relationship between fetal and maternal thyroid physiology

Understand the embryology and normal physiological function of the normal thyroid gland
May: Question 1

A 28-week-gestation female infant was born weighing 1,080 g. She received intravenous parenteral nutrition for the initial 2 weeks after birth. Enteral feedings were begun 5 days after birth but have been stopped several times because of feeding intolerance and a bout with necrotizing enterocolitis. She is currently 5 weeks old, weighs 1,130 g, and is tolerating 110 mL/kg per day of fortified breast milk.

Of the following, former premature infants with postnatal growth restriction are MOST likely, as adults, to have:

- higher body mass index
- hypotension
- insulin resistance
- malnutrition
- renal hypertrophy

You selected 2, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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Long-term follow-up studies on the neurodevelopmental outcomes associated with very low birthweight (VLBW) are remarkably encouraging. Although former VLBW infants have more health problems, greater developmental impairment, and lower educational achievement as adults, their self-reported level of self-esteem is similar to that of term controls. As these individuals reach adult years, consequences of being born early are being discovered in other areas of their general health.

Low-birthweight and VLBW infants born prematurely often have insufficient nutrient uptake during the fetal and early neonatal period because of abnormal placental transfer, limitations with parenteral supplementation, and gastrointestinal dysfunction. Often, at term adjusted age, these infants are more underweight for age than they were at birth, a condition called postnatal growth restriction. Upon reaching young adulthood, when compared with term, normally-nourished infants, metabolic differences have been described in former premature and undergrown infants that have been ascribed to the long-term effects of prematurity and/or low birthweight ("The Barker Hypothesis").

The Barker hypothesis suggests that adult disease may originate during fetal life. Furthermore, postnatal growth restriction experienced by most premature and VLBW infants may contribute to or exacerbate adult medical disorders. The low birthweight infant undergoes a marked environmental and nutritional disruption during the time of maximum growth velocity and continuing organogenesis when born prematurely. Both intrauterine and postnatal growth restriction may trigger
adaptations in circulation and/or metabolism that favor the supply of 
nutrients to the brain at the expense of other organs. Although modest 
adaptations may affect only fat deposition, resulting in normal head and linear growth, nutrient stress may affect organs such as the kidney, pancreas, liver, and muscle. Several mechanisms involving the hypothalamic-pituitary axis, neuroendocrine axis, renin-angiotensin system, alteration of gene expression (possibly because of oxidative stress), and epigenetic effects on mitochondrial genes have been postulated and are under study.

Epidemiologic studies of former low-birthweight and preterm infants have consistently found altered glucose metabolism and cardiovascular disease later in life. Statistically significant elevations in fasting glucose concentrations, postprandial and fasting insulin concentrations, and insulin resistance index occur among former low-birthweight infants when tested as adults (Table).

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</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.72</td>
<td>4.67</td>
<td>.08</td>
</tr>
<tr>
<td>2-h postprandial glucose, mmol/L</td>
<td>5.34</td>
<td>5.50</td>
<td>.02</td>
</tr>
<tr>
<td>Fasting insulin, mU/L</td>
<td>5.61</td>
<td>5.01</td>
<td>.001</td>
</tr>
<tr>
<td>2-h postprandial insulin, mmol/L</td>
<td>34.1</td>
<td>25.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Insulin resistance index†</td>
<td>1.18</td>
<td>1.04</td>
<td>.001</td>
</tr>
</tbody>
</table>

* Adapted from Hovi and colleagues (2007).

† Insulin resistance by homeostasis model assessment.

Changes in glucose metabolism were noted regardless of intrauterine growth status, suggesting an early neonatal component to the long-term changes in glucose metabolism. Although body mass indices were not found to be different between VLBW and term infants as adults, studies have related earlier emergence of type 2 diabetes to the adiposity rebound—the rapid increase in weight observed after a period of slower growth—that occurs in some infants. This pattern often may be seen after intrauterine growth restriction or postnatal growth restriction. Of note, decreased numbers of pancreatic beta cells and decreased beta-cell mass have been observed, depleting the capacity for insulin secretion to overcome insulin resistance. The degree to which this long-term pattern can be influenced by changes in early nutritional management will only be known as currently treated less malnourished neonates reach adolescence and adulthood.

Altered organogenesis has been noted among VLBW infants. Nephrogenesis continues until 34 to 36 weeks’ gestation. Persons with lower birthweights ultimately have fewer nephrons, and newborns are often exposed to potentially nephrotoxic treatments. Renal hypertrophy is not observed. Former low-birthweight infants also have been noted to have a higher incidence of hypertension than normal-birthweight infants. In addition to the kidneys and pancreas, altered growth patterns have been noted in the liver, muscle, and adipose tissue.
References:

Barker DJ, Eriksson JF, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol.* 2002;31:1235-1239


American Board of Pediatrics Content Specification(s):

Understand how extremes of intrauterine growth affect postnatal nutritional requirements

Recognize the effects of fetal programming on the prevalence of adult disorders

Understand the implications and management of fetal growth restriction

Understand the metabolic consequences of starvation in the neonatal period

Know how to diagnose and manage abnormalities of intrauterine growth rate
A 7-day-old female neonate, whose birthweight was 868 g and estimated gestational age at birth was 26 weeks, has evidence of hypothyroxinemia on newborn screening. Confirmatory laboratory tests of thyroid function reveal the following plasma concentrations.

You are discussing with medical students the regulation of thyroid function during fetal life and its implications in infants delivered prematurely.

Of the following, the mechanism of regulation of fetal thyroid function EARLIEST to mature during gestation is:

1. alternate pathways of thyroid hormone metabolism
2. deiodination of iodothyronines
3. hypothalamic-pituitary-thyroid axis
4. thyroid hormone binding proteins
5. Wolff-Chaikoff iodide regulation

You selected 1, the correct answer is 1.

The infant in this vignette has low plasma concentrations of total and free thyroid hormones, thyroid-stimulating hormone (TSH), and thyroxine-binding globulin (TBG), which are characteristic of transient hypothyroxinemia of prematurity. This disorder is a result of immature development of fetal thyroid function.

During fetal life, thyroid hormones are unmeasurable until approximately 20 weeks of gestation (Figure 1).
Figure 1: Thyroid hormones during human fetal development

Thyroid hormone tetraiodothyronine (thyroxine, T4) appears at approximately 20 weeks of gestation and its plasma concentration increases linearly thereafter until term. Thyroid hormone triiodothyronine (T3) appears at approximately 30 weeks of gestation and its plasma concentration increases linearly thereafter until term. The appearance of TSH and increase in its plasma concentration during gestation precedes the rise in circulating concentrations of thyroid hormones. In contrast to T4 and T3, the plasma concentration of reverse triiodothyronine (rT3) is high during fetal life and declines with advancing gestation. These findings suggest that the regulation of fetal thyroid function—promotion of an optimal balance between production and disposal of thyroid hormones—is developing during fetal life and, in general, the mechanisms for preventing thyroid hormone excess are developed earlier than those for preventing thyroid hormone deficiency.

Among the mechanisms of regulation of fetal thyroid function, the alternate pathways of thyroid hormone metabolism mature earliest, by approximately 19 weeks of gestation. These pathways include T4 conjugation with sulfate or glucuronide, T4 deamination and decarboxylation, and ether-link cleavage. Among these pathways, the production of sulfate conjugates, catalyzed by the enzyme phenol sulfotransferase, is the major disposal pathway for both T4 and T3. T4 sulfate is detectable in human fetal blood by 19 weeks of gestation.

To understand thyroid function regulation by deiodination of iodothyronines, it is important to examine the synthesis of the thyroid hormones. Thyroid hormone synthesis involves three critical steps: uptake of iodide, iodination of tyrosine, and deiodination of thyronines. The thyroid uptake of iodide from the circulating pool of iodide is under the influence of TSH. The iodination of tyrosine involves incorporation of iodine in specific positions within the tyrosyl ring of thyroglobulin, a glycoprotein synthesized by the endoplasmic reticulum in thyroid follicle cells. This iodination of tyrosine is catalyzed by the enzyme thyroid peroxidase. The resultant iodothyrosines are monoiiodothyrosine (3-iiodothyrosine) (Figure 2A) and diiodothyrosine (3,5-diiodothyrosine) (Figure 2B). These iodothyrosines have no hormonal activity.
Coupling of the iodothyronines, under the influence of thyroid peroxidase, results in the formation of iodothyronines. Each iodothyronine has two rings, an inner tyrosyl ring with positions designated as 3 and 5, and an outer phenolic ring with positions designated as 3' and 5'. T₄ (3,3',5,5'-tetraiodothyronine) (Figure 2C) is the principal product of thyroid hormone synthesis.

It has minimal biologic activity and acts mainly as a precursor of active thyroid hormone. Removal of iodine (deiodination) from specific positions within the tyrosyl and phenolic rings of T₄, under the influence of deiodinase, is required for the formation of functional thyroid hormones. T₃ (3,3',5-triiodothyronine) (Figure 2D) is derived by 5'-deiodination; it is the most biologically active form of thyroid hormone.
rT₃ (3,3',5'-triiodothyronine) (Figure 2E) is derived by 5-deiodination; it is biologically inactive. Further deiodination results in the formation of diiodothyronines and monoiodothyronines, which have no biological activity.

The process of deiodination of thyronines is critical for balancing thyroid function; 5'-deiodination is predominant when active thyroid hormone is needed, whereas 5-deiodination prevails when thyroid function needs to be suppressed. Fetal thyroid metabolism early in gestation is oriented largely to production of inactive hormones via predominant 5'-deiodination of T₄ to rT₃. The 5'-deiodination of T₄ to active T₃ does not manifest until approximately 30 weeks of gestation, increasingly around the time of birth.

The hypothalamic-pituitary-thyroid (HPT) axis (Figure 3) represents a feedback loop of thyroid hormone regulation. According to this axis, low circulating concentrations of thyroid hormones stimulate the hypothalamus, specifically the paraventricular nucleus, to secrete thyrotropin-releasing hormone (TRH).
The TRH stimulates the thyrotropic cells of the anterior pituitary to secrete TSH. The TSH stimulates the thyroid gland to restore the circulating concentrations of thyroid hormones within the normal range. Conversely, excess thyroid hormones in circulation suppress the hypothalamic TRH, which inhibits the pituitary TSH and lessens the stimulatory effect of TSH on the thyroid gland, normalizing the circulating concentrations of thyroid hormones. This central regulation of thyroid function via the HPT axis does not appear until approximately 26 weeks of gestation in the human fetus; it matures during the third trimester of pregnancy. The low plasma concentration of TSH in the face of low plasma concentrations of all thyroid hormones in the infant in this vignette is consistent with immaturity of the HPT axis.

Most of the circulating thyroid hormones are bound to plasma proteins. Only about 0.03% of total T₄ and 0.3% of total T₃ is present in free or unbound form. The major thyroid-hormone-binding proteins are TBG, transthyretin, and albumin. The normal distribution of T₄ among these proteins is approximately 80% bound to TBG, 15% bound to transthyretin, and 5% bound to albumin. This protein binding of thyroid hormones serves at least two functions. First, by creating a flexible extrathyroidal reservoir of thyroid hormones, the thyroid-hormone-binding proteins serve to safeguard the body from the effects of abrupt fluctuations in hormonal secretion and disposal. Second, by imparting macromolecular properties to the small iodothyronine molecules, the thyroid-hormone-binding proteins may limit the urinary loss of these iodothyronines. The hepatic synthesis of thyroid-hormone–binding proteins matures during the third trimester of pregnancy in the human fetus, making a preterm infant vulnerable to fluctuations in thyroid function and to urinary loss of thyroid hormones.

Iodide, the principal substrate of the thyroid follicle cell in the synthesis of thyroid hormones, regulates its own metabolism and, consequently, thyroid function, independent of TSH. This iodide regulation, called Wolff-Chaikoff regulation, involves the capacity of the thyroid follicle cell to increase iodide trapping in the presence of low plasma iodide concentrations, and to decrease iodide trapping in the presence of iodide excess. Upon uptake of iodide by the thyroid follicle cell, its oxidation to iodine, mediated by thyroid peroxidase, is a critical prerequisite for iodination of tyrosine in thyroid hormone synthesis. In the mature thyroid follicle cell, iodide can self-regulate its own oxidation to iodine depending on the status of the thyroid function.
This thyroid autoregulation develops only after 36 to 40 weeks of gestation in the human fetus. The preterm infant, thus, is unable to regulate the thyroid function in the presence of iodide deficiency or excess.

References:


American Board of Pediatrics Content Specification(s):

Know the physiological roles of the hormones and other proteins involved in the regulation of thyroid function

Understand the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction

Understand the causes of transient hypothyroidism in the neonate
A 4-day-old, 35-week-gestation male infant with intrauterine growth restriction is referred to you for evaluation and management of mixed hyperbilirubinemia. His mother is being treated with thyroxine after thyroid ablation 5 years ago for Graves disease. Delivery was vaginal and uncomplicated. After birth, the infant is found to be symmetrically growth restricted with marked hepatosplenomegaly, petechiae, icterus, and small anterior fontanel (0.5 cm diameter). Tachypnea and tachycardia are also present. He is vigorous and no congenital anomalies are present. Stools are pale white in color. Laboratory and radiology investigations available include the following:

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>Markedly elevated</td>
</tr>
<tr>
<td>Conjugated bilirubin</td>
<td>Markedly elevated (3.5% of total)</td>
</tr>
<tr>
<td>Unconjugated bilirubin</td>
<td>Moderately elevated</td>
</tr>
<tr>
<td>Transaminases</td>
<td>Minimally elevated</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Elevated</td>
</tr>
<tr>
<td>γ-glutamyl transferase</td>
<td>Normal</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Elevated</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>Elevated</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>Elevated</td>
</tr>
<tr>
<td>Platelets</td>
<td>Low</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Low</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Normal</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Normal</td>
</tr>
<tr>
<td>Galactose-1-phosphate undecyl transferase activity</td>
<td>Normal</td>
</tr>
<tr>
<td>α1-antitrypsin</td>
<td>Normal</td>
</tr>
<tr>
<td>Sweat chloride</td>
<td>Normal</td>
</tr>
<tr>
<td>Free thyroxine</td>
<td>High</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone</td>
<td>Low</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Mild cardiomegaly, diminished vascularity</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Mild pulmonary hypertension</td>
</tr>
<tr>
<td>Abdominal sonogram</td>
<td>Normal, gallbladder present, no dilation of hepatic ducts, biliary sludge, or choledochal cyst</td>
</tr>
<tr>
<td>Bacterial cultures</td>
<td>No growth</td>
</tr>
<tr>
<td>Viral serologies and cultures</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Of the following, the study that is MOST likely to confirm the diagnosis in this infant is:

1. *ABCB11* gene mutation analysis (lymphocytes)
2. Cytomegalovirus culture (urine)
3. Fumarylacetoacetate hydroxylase activity (lymphocytes)
The presence of thyroid-stimulating antibodies in the infant in this vignette will confirm the diagnosis of congenital hyperthyroidism. Maternal Graves disease, high thyroxine concentration, and low thyroid-stimulating hormone concentration raise suspicion about congenital hyperthyroidism as the cause for the clinical findings in this infant. Intrauterine growth restriction, cardiomegaly associated with congestive heart failure, hepatosplenomegaly, small anterior fontanel, petechiae, goiter, proptosis, hyperkinesis, diarrhea, and poor growth are reported in neonates with this disorder.

Infants born to mothers receiving antithyroid medications, such as propylthiouracil, may become biochemically and clinically hyperthyroid during the first weeks after birth as the antithyroid medications are metabolized. In contrast, infants born to mothers whose thyroid gland has been ablated may become hyperthyroid in utero because of the ongoing production and transplacental passage of thyroid-stimulating antibodies by the mother, as occurred in the infant in this vignette.

Cholestatic jaundice is an unusual finding in congenital hyperthyroidism. Although the mechanism is unclear, the cholestasis improves with treatment and recovery from hyperthyroidism. Immaturity of bile formation and flow in neonates is reflected by impaired hepatic uptake of bile salts (the primary stimulus for bile flow), smaller bile salt pool size, and lower rates of absorption in the ileum (versus the adult). These deficiencies are described by the term physiologic cholestasis (or physiologic hypercholanemia) of infancy. It is likely that pituitary hormones affect bile synthesis and flow because of the association of cholestasis with hypopituitarism. However, the specific effect of pituitary hormones, specifically thyroxine, on bile metabolism is yet to be determined.

It could be conjectured that the taurine conjugated bile acids and precursors that predominate in the fetus, rather than the glycine conjugates that predominate in the older child and adult, may be overproduced in response to the hypermetabolic response to high thyroxine concentrations. These taurine-conjugated bile acids may then accumulate because of immature bile metabolism in the neonate and impair the metabolic and cellular functions of the hepatocyte.

The presence of intrauterine growth restriction, coagulopathy, and elevated liver function results, including the conjugated fraction of bilirubin, is consistent with a number of congenital infections, including cytomegalovirus, toxoplasmosis, human immunodeficiency virus, parvovirus B19, and herpes simplex. Absence of maternal or placental evidence of congenital infection usually prompts a search for the other common and easily evaluated causes for neonatal cholestasis, especially if early recognition and treatment are important to reduce morbidity. The causes of neonatal cholestasis include:

- biliary atresia (most common)
- other obstructive biliary tract disorders (such as choledochal cysts, paucity of bile ducts)
- inherited disorders (such as α1-antitrypsin deficiency, cystic fibrosis)
- bacterial infections (such as sepsis and urinary tract infections)
- galactosemia
- hypothyroidism
- idiopathic hepatitis

If clinical or laboratory studies are inconclusive or suggestive of other diagnoses, additional
evaluation is indicated for other inborn errors of metabolism (such as tyrosinemia, fructosemia, peroxisomal disorders, progressive familial intrahepatic cholestasis, bile salt synthetic defects, congenital hemochromatosis), endocrinopathies (such as hypopituitarism, hyperthyroidism), syndromes (such as Alagille syndrome), and toxic exposures (such as drugs, parenteral nutrition).

ABCB11 gene mutation analysis determines the presence of mutations in the gene responsible for progressive familial intrahepatic cholestasis type 2 (PFIC2). The ABCB11 gene is responsible for the activity of the bile salt export pump located on the canalicular membrane of the hepatocyte. Like progressive familial intrahepatic cholestasis type 1 (PFIC1, mutation of the ATP8B1 gene), PFIC2 is inherited in an autosomal recessive pattern and the spectrum of disease can be variable. However, severe cholestasis with pruritus, malabsorption, greasy stools, and failure to thrive may present in the first months after birth. If untreated, cirrhosis, hepatic failure, and death may occur during infancy or early childhood. The diagnosis is usually determined on clinical and laboratory findings with low or normal concentrations of g-glutamyltranspeptidase (GGT). In most disorders that cause cholestasis, GGT is elevated. Cholestasis with hyperthyroidism is one of the few disorders associated with normal or low GGT, as in the infant in this vignette.

Isolation of cytomegalovirus (CMV) from fibroblast tissue cultures of urine or saliva is the standard reference method to determine the presence of CMV. Modifications of the tissue culture method by the addition of monoclonal antibodies to CMV-specific early antigens (shell vial assay, microtiter plate immunofluorescent antibody assay) may allow diagnosis to be established within 24 hours. Such modifications have shown high sensitivity and specificity. DNA hybridization methods are reliable but limited if the titer of virus is less than $10^3$ infective doses per milliliter. The polymerase chain reaction amplification method for detecting CMV in many tissue or body fluid specimens is highly sensitive and specific. A modification for use of dried filter paper specimens is also available for retrospective diagnosis. Detection of antigenemia using CMV-specific monoclonal antibodies is also available but sensitivity and specificity are not superior to other methods. Serologic analysis of the immune response to CMV is complicated by individual variations in development of IgG and IgM antibodies and lower sensitivity and specificity than viral culture methods.

A diagnosis of tyrosinemia type 1 is confirmed by measurement of fumarylacetoacetate hydroxylase activity in lymphocytes, erythrocytes, or liver biopsy specimens. A presumptive diagnosis is determined by the onset in early infancy of hepatic failure, hepatomegaly, hemorrhage, vomiting, hypoglycemia, Fanconi-like syndrome (normal anion gap acidosis, hyperphosphaturia, hypophosphatemia), mixed hyperbilirubinemia, and elevations of serum transaminases and a-fetoprotein (even in cord blood specimens suggesting in utero liver dysfunction). These findings usually are precipitated by an intercurrent illness and catabolic state. Increased plasma tyrosine and methionine concentrations and elevated serum and urine succinylacetocacetate and succinlylacetone are diagnostic. Tyrosinemia type 1 is rare (1:110,000 live births) outside Quebec, Canada (1:1,846 live births), transmitted in an autosomal recessive fashion, treatable with 2-(nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione and liver transplantation, and carries a high risk of hepatocellular carcinoma (37% of cases).

Alagille syndrome is diagnosed with Jagged-1 mutation analysis. Eighty-eight percent of affected individuals have abnormalities in the Jagged-1 gene. Fluorescence in situ hybridization for microdeletions of chromosome 20p12 will detect another 7% of affected patients and mutation analysis of the NOTCH2 gene in present is 1% of affected individuals. Alagille syndrome is inherited as an autosomal dominant disorder and is characterized by:

- Chronic cholestasis
- Peripheral branch pulmonary stenosis and other cardiac defects
- Paucity of bile ducts (beginning in childhood)
- Butterfly vertebrae and other skeletal abnormalities
- Characteristic facies (broad forehead, deep-set eyes, triangular facies)
- Eye abnormalities (posterior embryotoxon = prominent Schwalbe ring in the anterior chamber of the eye)
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


American Board of Pediatrics Content Specification(s):

Identify the effect of maternal immunologic disease with transplacental passage of immunoglobulins and its treatment on the fetus

Understand the relationship between fetal and maternal thyroid physiology

Understand the differential diagnosis, evaluation, and approach to management of mixed forms of jaundice

Recognize the effects on the fetus of maternal endocrine disorders (other than diabetes mellitus) and their management

Identify the etiology and clinical manifestations of congenital hyperthyroidism

Know the laboratory features and treatment of congenital hyperthyroidism

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids

Understand the diagnostic criteria of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Ebstein-Barr virus, and varicella virus

Know the various laboratory and radiographic techniques to diagnose metabolic and familial causes of cholestasis in the neonate
An infant born at 38 weeks' gestation is evaluated for low birthweight (1,820 g). Length is at the 10th percentile and head circumference at the 50th percentile on the growth chart. The infant's mother is a 28-year-old primigravida, whose pregnancy has been complicated by severe preeclampsia.

Of the following, the outcome MORE likely to be found later in life in the infant in the vignette than in infants with normal growth is:

1. growth hormone deficiency
2. insulin resistance
3. mental retardation
4. short stature
5. subcutaneous adiposity

You selected 2, the correct answer is 2.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The metabolic syndrome, although variably defined, is composed principally of insulin resistance, hyperinsulinemia, visceral adiposity, dyslipidemia, and systemic hypertension. Ischemic heart disease and overt type 2 diabetes mellitus may develop. Systemic inflammation, hypercoagulability, and endothelial dysfunction are also observed in the spectrum of this disorder. About 20% to 30% of adults are affected and the prevalence is increasing. Teenagers are also being diagnosed with the metabolic syndrome at an alarming frequency. Because morbidity and mortality during adulthood are substantial, research and development of strategies to prevent or treat associated pathophysiologic aberrations are receiving emphasis by neonatologists and internal medicine specialists alike.

Multiple metabolic and physiologic abnormalities underlie the metabolic syndrome. Insulin resistance and abnormal adipose tissue metabolism are common, but not essential, features (Figure 1).

Figure 1: Pathogenic mechanisms contributing to the metabolic syndrome (adapted from Batsis et al [2007])
A large body of epidemiologic and animal model evidence indicates that low birthweight, especially presenting as intrauterine growth restriction (IUGR) as in the infant in this vignette, is associated with a high risk for developing the metabolic syndrome and its complications. The risk for metabolic syndrome in small-for-gestational-age infants during young adulthood is low (2.3%) but is sixfold higher than in those who were appropriate for gestational age (0.4%). Landmark studies have demonstrated associations between low birthweight and obesity, hypertension, hypertriglyceridemia, cardiovascular disease (myocardial infarction, stroke), impaired glucose tolerance, and type 2 diabetes mellitus.

It is important to recall that size at birth is a poor proxy for IUGR. Small size is associated with many causes, not all of which may have implications for adult disease. For example, infants whose birthweights are lower than the 10th percentile on growth grids are often constitutionally small but do not have IUGR. These normal-growth but small infants may not be at higher risk for adult morbidity than those born with IUGR. Additional research is needed to clarify which populations of infants born “small” are at risk for “adult” diseases.

The underlying mechanisms for later development of metabolic syndrome in infants with IUGR are unclear. These mechanisms likely involve fetal programming of metabolic pathways and organ development in response to limited nutrient/oxygen delivery and pathologic insults (Figure 2).

Figure 2: The thrifty phenotype hypothesis (reprinted with permission from Fernandez-Twinn and Ozanne [2006])
The "thrifty phenotype" hypothesis describes in utero programming of fetal metabolic systems and physiologic adaptations in response to life-threatening maternal stress, infection, undernutrition, placental dysfunction, and exposure to alcohol and tobacco. After birth, these metabolic and physiologic adaptations then become a liability during times of nutrient excess.

Changes in the hypothalamic-pituitary-adrenal axis are hypothesized to play a pivotal role in fetal adaptations but oxidant stresses also likely play important roles. The combination of increased fetal catabolism and subsequent metabolic reprogramming causes growth restriction. Specific findings in affected infants include reduction in pancreatic beta-cell mass and function; growth hormone hypersecretion (induces insulin resistance); abnormal muscle, liver, and fat development (visceral rather than subcutaneous adiposity); changes in adrenal and neuroendocrine production; and reduction in glomerular number. Genetic and epigenetic changes occur and account, in part, for risk transmission through subsequent generations of offspring. Insulin resistance, hypertension, visceral adiposity, and other findings of the metabolic syndrome result. As the infant grows, occult physiologic and metabolic abnormalities exist but overt signs and symptoms may only become apparent or be triggered during the teenage years and adulthood.

An interesting parallel has been described between full-term infants with IUGR and extremely preterm infants. Both experience undernutrition during the last "trimester" of fetal life. The preterm infant fails to grow during the first weeks after birth because of limited nutrient intake and medical illness. During this time, low concentrations of insulinlike growth factor 1 (IGF-1), an important regulator of growth, stimulate excessive secretion of growth hormone. The adrenal hormone axis is often upregulated because of stress and, combined with a large supply of growth hormone, causes insulin resistance. The addition of exogenous glucocorticoids exacerbates these pathophysiologic phenomena. In the presence of overnutrition and inhibition of important adipocyte metabolic pathway components (such as beta3-adrenoreceptors), fat is preferentially deposited in visceral sites within the mesentery and abdomen rather than in subcutaneous sites. This gives infants the appearance of truncal obesity with relatively thin extremities. Protein supplementation to raise IGF-1 levels has the potential to reduce growth hormone hypersecretion and insulin resistance. Supplementation with very-long-chain polyunsaturated fatty acids (such as eicosapentaenoic acid and docosahexaenoic acid) has been found to reduce production of proinflammatory mediators that also cause insulin resistance. Additional protein and very-long-chain fatty acid supplementation are promising interventions to mitigate the evolution of the physiologic impairments that may lead to the metabolic syndrome in recovering preterm infants and full-term infants with IUGR.

Although there are conflicting reports, infants who are born at term and severely growth
restricted are found to have IQs similar to those of infants with normal growth. Nevertheless, such infants with IUGR are at higher risk for school failure because of behavioral disorders (especially attention deficit disorder) and learning disabilities. In contrast, preterm infants with severe IUGR have higher rates of cognitive, motor, and neurologic deficits than preterm infants without IUGR. Interestingly, such infants have lower rates of cerebral palsy.

Growth patterns in infants with IUGR vary with the cause of the growth restriction. Infants with moderate IUGR and uncomplicated medical courses, such as the infant in the vignette, usually reach normal height. In comparison, infants with severe IUGR are frequently shorter and lighter through adolescence.

References:


Fernandez-Twinn DS, Ozanne SE. Mechanisms by which poor early growth programs type-2 diabetes, obesity and the metabolic syndrome. *Physiol Behav.* 2006;88:234-243


**NY Acad Sci. 2006;1092:138-147**


**American Board of Pediatrics Content Specification(s):**

- Recognize that there may be a period of catch-up growth in SGA infants
- Understand the differences in body composition between SGA, LGA, and AGA infants
- Know the nutritional requirement before and during pregnancy and the impact on fetal growth and development
- Understand the complications and management of fetal growth restriction
A 26-week-gestation premature female infant is born after spontaneous labor and rupture of membranes. Her mother was healthy before the onset of labor and had no history of a thyroid disorder. The birthweight was 900 g. The infant had respiratory distress that was treated with three doses of surfactant and severe hypotension that was treated with dopamine and hydrocortisone. She was supported with assisted ventilation for the first 10 days and had persistent oxygen dependency. She was treated for suspected pneumonia and/or sepsis. A state screening test conducted at 3 days of age and before any transfusion reveals a thyroxine (T₄) concentration of 2.8 μg/dL (36 nmol/L), just below the normal range for age, and a normal thyroid-stimulating hormone (TSH) concentration of 19 mIU/L. Confirmatory serum studies are ordered, including T₄ and free thyroxine (FT₄). The FT₄ concentration was in the low-normal range.

Of the following, the MOST appropriate management plan at this time would be to:

1. follow clinically; no need to recheck values if no signs or symptoms
2. initiate L-thyroxine treatment and continue for life
3. initiate L-thyroxine treatment; discontinue in 3 years
4. recheck TSH at 2 weeks and 6 weeks; if TSH becomes abnormal, treat
5. recheck TSH in 2 weeks; if TSH still normal, no further testing needed

You selected 4, the correct answer is 4.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Congenital hypothyroidism occurs in 1 in 3,000 to 1 in 4,000 newborn infants. It is either primary, when it involves a disorder of the thyroid gland itself (malformation or inborn error of thyroid synthesis), or secondary, involving a disorder of thyrotropin (TSH) production or release (central). The primary form occurs more frequently and is usually associated with elevated serum TSH values soon after birth. The latter is usually accompanied by other pituitary hormone deficiencies.

Most infants with an initially low thyroxine (T₄) and normal TSH concentration have a normal free thyroxine (FT₄) concentration and subsequent thyroid function test results are normal. Some experts have suggested following them clinically for signs of hypothyroidism. However, some of these infants have true hypothyroidism, which will result in irreversible mental retardation; therefore, the preferred management is to repeat laboratory studies until the infant is clearly hypothyroid (elevated TSH) or is at least 6 weeks old, because the delay in TSH elevation may persist until then. L-thyroxine therapy should not be started for a low T₄ value during significant illness because these low values may represent the euthyroid sick syndrome, in which case thyroxine treatment may be harmful.
Some infants with normal TSH but low T\textsubscript{4} values may have true thyroid insufficiency. This profile is seen in 3% to 5% of newborn infants. The pattern may result from hypothalamic immaturity and is most commonly seen among preterm infants. Low T\textsubscript{4} with normal TSH may also occur in central hypothyroidism (1 in 25,000 to 1 in 50,000 newborn infants) or with true primary hypothyroidism and delayed TSH elevation (1 in 100,000 newborns, but more prevalent among very-low-birthweight infants).

Primary congenital hypothyroidism with delay in TSH elevation also can be seen in infants who have significant illnesses that are often associated with exposure to exogenous iodine (from povidone antiseptic or intravenous contrast solutions), glucocorticosteroids, dopamine, and/or antibiotics. The duration of the delay in TSH elevation has been reported to vary from 11 to 176 days among very-low-birthweight infants, but rarely exceeds 6 weeks. Among term infants with delayed TSH increase, the delay varied from 3 to 94 days and congenital heart disease is more common than otherwise expected. Once the TSH rises, L-thyroxine replacement therapy is recommended.

If T\textsubscript{4}, FT\textsubscript{4}, and TSH concentrations are all low, then central or secondary hypothyroidism should be considered. Isolated TSH-releasing hormone deficiency may cause low-normal T\textsubscript{4} and low or normal TSH concentrations. Central hypothyroidism has been reported in association with severe birth trauma or asphyxia, often with other pituitary hormone deficiencies.

A few infants with abnormal screening values will have true transient hypothyroidism. These infants have transient elevation of TSH, unlike the infant in the vignette, and will have normal serum T\textsubscript{4} and TSH concentrations later. This condition occurs in 1 in 50,000 newborns in North America. It also is more common in premature infants but can occur in apparently healthy term infants. This condition can be caused by intrauterine exposure to antithyroid medications, maternal antibodies to thyrotropin receptors, abnormal thyrotropin receptors (mutations), iodine deficiency during pregnancy, or recent exposure to excess iodides. These causes can be identified by obtaining an appropriate history.

Because transient hypothyroidism can interfere with brain development, this condition requires thyroid replacement therapy. To help decide whether the condition is transient or permanent, the thyroid medication can be stopped for at least a month after the third birthday. This will not interfere with long-term neurodevelopment and should help the clinician decide whether it is necessary to continue replacement therapy.

**References:**


Shaikh MG, Anderson JM, Hall SK, Jackson MA. Transient neonatal hypothyroidism due to a maternal vegan diet. *J Pediatr Endocrinol Metab.* 2005;18:111-113

American Board of Pediatrics Content Specification(s):
Understand the causes of transient hypothyroidism in the neonate

Understand the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction
A female infant with a birthweight of 4,785 g was delivered by a 34-year-old multiparous obese Native American woman whose pregnancy was complicated by gestational diabetes. An emergency cesarean section was performed for shoulder dystocia. Physical examination reveals a large-for-gestational-age infant with Erb palsy.

Of the following, fetal macrosomia in diabetic pregnancies is MOST characterized by its:

1. detectability by ultrasound in the first trimester
2. higher risk among mothers with pregestational type 1 diabetes
3. lack of impact on growth velocity after 2 weeks of age
4. lower risk for shoulder dystocia than nondiabetic macrosomia
5. reduction by strict glycemic control in second and third trimesters

You selected 2, the correct answer is 5.

Macrosomia, defined as birthweight above the 90th percentile for gestational age or birthweight greater than 4,000 g occurs in 15% to 45% of diabetic pregnancies compared with 8% to 14% of normal pregnancies. It is a risk factor for intrapartum injury (shoulder dystocia, brachial plexus palsy, and asphyxia) and for cesarean delivery.

As hypothesized by Pedersen, the increase in fetal growth in a diabetic pregnancy is the result of increased maternal glucose concentrations. Glucose crosses the placenta and results in fetal hyperglycemia and subsequent hyperinsulinemia. This hyperinsulinemia affects primarily insulin-sensitive tissues such as fat. The risk of macrosomia is similar for all classes of diabetes (type 1, type 2, and gestational), suggesting that first-trimester metabolic control has less effect on fetal growth than glycemic regulation in the second and third trimesters. Postprandial blood glucose concentrations in the second and third trimesters of pregnancy are strongly predictive of both birthweight and overall percentage of macrosomic infants. Furthermore, it has been shown that strict glycemic control in the second and third trimesters may reduce the fetal macrosomia rate to near baseline. However, other authors have shown that macrosomia is determined primarily by early diabetes control and suggested that strict blood glucose control in the first and second trimesters may reduce the incidence of large-for-gestational-age infants.

The macrosomic infant of a diabetic mother (IDM) follows a unique pattern of in utero growth compared with fetuses in euglycemic pregnancies. During the first trimester, no differences in size between diabetic and nondiabetic fetuses are detectable by ultrasound measurements. However, after 24 weeks (20 weeks in one study) the abdominal circumference of the fetus of a
diabetic pregnancy begins to grow at a rate above normal because of deposition of fat in the abdominal and interscapular areas and visceral organ hypertrophy (liver, heart, adrenals, pancreas). Of significance, head and femur growth of IDM fetuses are similar to those of normal fetuses. This central deposition of fat is a key characteristic of diabetic macrosomia and combined with the lack of increase in head size, is responsible for the higher incidence of shoulder dystocia in these cases. Among infants with birthweights more than 4,000 g, the incidence of shoulder dystocia is 16% in diabetic pregnancies compared with 3% among nondiabetic pregnancies.

The higher growth velocity seen in fetal life during a diabetic pregnancy may extend into childhood and adult life. By 8 years of age, approximately half of the IDMs are above the 90th percentile for weight. It is believed that offspring of a diabetic pregnancy have a permanent derangement of glucose-insulin kinetics, resulting in a higher incidence of impaired glucose tolerance and type 2 diabetes.

References:


American Board of Pediatrics Content Specification(s):

Know the effect of diabetes mellitus and its treatment on the fetus

Know the causes of maternal and neonatal complications and the management of abnormal presentations, such as breech, shoulder dystocia, etc

Understand the implications of fetal macrosomia
A pregnant woman who initially presented at 8 weeks’ gestation had her pregnancy dates confirmed by crown-rump length measurement. Genetic screening results were normal and maternal weight gain and overall health were good. Currently, at 33 weeks’ gestation, the uterine fundal height is 29 cm. Repeat ultrasonography reveals an estimated fetal weight of 1,200 g and a relatively small, low-lying placenta, leading you to consider the placental role in fetal growth.

Of the following, the MOST important placental hormone involved in regulating the growth of the fetus is:

1. corticotropin-releasing hormone
2. estrogen
3. human chorionic gonadotropin
4. human placental lactogen
5. progesterone

You selected 3, the correct answer is 1.

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The human placenta plays a pivotal role in fetal growth. It must integrate fetal demand with maternal substrate supply. In addition to transferring nutrients and waste products, the placenta has metabolic and endocrine functions that assist with fetal growth. In its role as an endocrine organ, it produces peptide hormones, such as human chorionic gonadotropin (hCG), human growth hormone variant (hGHv), human placental lactogen (hPL), insulinlike growth factors (IGFs), and corticotropin-releasing hormone (CRH), as well as steroid hormones, such as estrogens, progesterone, and glucocorticoids. Depending on the compound, hormones are released into the fetal and/or maternal circulations.

The placental hormone important for fetal growth regulation required in this vignette is hPL. hPL is secreted into both the maternal and fetal circulations after 6 weeks’ gestation. In the pregnant woman, hPL stimulates production of IGF, ultimately resulting in an increase in glucose and amino acid availability to the fetus. In the fetus, hPL modulates embryonic development and influences fetal growth by stimulating production of other hormones, such as IGFs and insulin, which are important in cellular proliferation and growth.

Corticotropin-releasing hormone is produced by the placenta and secreted into the fetal circulation, increasing fetal cortisol production and assisting with fetal lung maturation. CRH is also secreted into the maternal circulation. Because peak CRH concentrations are observed at the time of labor, it is postulated that CRH is an important trigger for the onset of labor.
Although the placenta secretes estrogen in increasing amounts throughout pregnancy, estrogen is not directly involved in fetal growth. It has many functions, including regulation of progesterone, maturation of fetal organs, proliferation of the uterine endometrium, and stimulation of fetal adrenocorticotropic hormone secretion.

During early pregnancy, hCG enters the maternal circulation and stimulates progesterone production in the corpus luteum. It does not play a role in fetal growth. Maximal concentrations of hCG are reached at week 8 of gestation and by week 13, the placental production of progesterone supports the continuing pregnancy.

Placental production of progesterone begins approximately 35 to 47 days after ovulation. Although some studies have shown correlations between maternal progesterone concentrations and birthweight, progesterone has minimal direct effect on fetal growth. Instead, progesterone is necessary for maintaining a quiescent uterus. It also has antiinflammatory and immunosuppressive abilities, protecting the fetus from immunologic rejection by the mother.

Human GHv is another hormone produced by the placenta that plays an indirect role in fetal growth. However, unlike hPL, it is only secreted into the maternal circulation. During pregnancy, maternal pituitary GH production is suppressed and hGHv becomes the dominant GH in the maternal circulation. Human GHv can stimulate IGF production in the pregnant woman and influence fetal growth by increasing the nutrient availability to the fetus. Interestingly, maternal serum concentrations of hGHv are reduced in growth-restricted fetuses.

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References:


American Board of Pediatrics Content Specification(s):
Understand the hormonal factors that affect intrauterine growth
Understand the fetal factors that affect intrauterine growth
A 14-day-old male neonate, whose birthweight was 952 g and estimated gestational age at birth was 27 weeks, has sudden onset of apnea and bradycardia, temperature instability, lethargy, and poor skin perfusion. He requires mechanical ventilation, a high fraction of inspired oxygen, vasopressor support, and intravenous nutrition. He also is receiving broad-spectrum antibiotics for suspected sepsis. Thyroid function tests, performed as a part of a research study, reveal the following plasma concentrations.

<table>
<thead>
<tr>
<th>Thyroid Function Tests</th>
<th>Patient Results (SI Values)</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thyroxine, µg/dL (nmol/L)</td>
<td>8.0 (104)</td>
<td>8.0-16.0 (104-208)</td>
</tr>
<tr>
<td>Total triiodothyronine, ng/dL (nmol/L)</td>
<td>39 (0.6)</td>
<td>80-200 (1.2-3.1)</td>
</tr>
<tr>
<td>Total reverse triiodothyronine, ng/dL (nmol/L)</td>
<td>98 (1.5)</td>
<td>15-65 (0.2-1.0)</td>
</tr>
<tr>
<td>Free thyroxine, ng/dL (pmol/L)</td>
<td>4.3 (56)</td>
<td>2.0-4.0 (26-52)</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, ml/U/L</td>
<td>0.4</td>
<td>0.5-10.0 (0.5-10.0)</td>
</tr>
<tr>
<td>Thyroxine-binding globulin, mg/dL (nmol/L)</td>
<td>1.2 (192)</td>
<td>1.5-3.0 (240-480)</td>
</tr>
</tbody>
</table>

Of the following, the abnormal thyroid function in this infant MOST likely involves:

1. coupling enzyme
2. 5'-deiodinase
3. thyroid peroxidase
4. thyroid-stimulating hormone
5. thyroxine-binding globulin

You selected 2, the correct answer is 2.

The clinical features and thyroid function tests in the infant in this vignette are consistent with the diagnosis of euthyroid sick syndrome (ESS), also called nonthyroidal illness or low T₃ syndrome. In ESS, thyroid function is altered by a systemic illness in the absence of an intrinsic thyroid glandular disease.

To understand thyroid function in ESS, it is important to examine the synthesis of the thyroid hormones. Thyroid hormone synthesis involves three critical steps: uptake of iodide, iodination of tyrosine, and deiodination of thyronines.

In ESS, the iodide uptake by the thyroid gland under the influence of TSH is usually normal. Likewise, the iodination of tyrosine and the formation of iodothyronines under the influence of thyroid peroxidase and coupling enzyme are usually normal. Also although the synthesis of TBG is usually normal, the binding of the thyroid hormone to TBG is decreased. The problem in ESS...
removes iodine (deiodination) from specific positions within the tyrosyl and phenolic rings of T4, under the influence of deiodinase, is required for the formation of functional thyroid hormones. Triiodothyronine (3,3',5-triiodothyronine) (T3) is derived by 5'-deiodination; it is the most biologically active form of thyroid hormone. Reverse triiodothyronine (3,3',5'-triiodothyronine) (rT3) is derived by 5-deiodination; it is biologically inactive. Further deiodination results in the formation of diiodothyronines and monoiodothyronines, which have no biologic activity. The process of deiodination of thyronines is critical for balancing thyroid function; 5'-deiodination is predominant when active thyroid hormone is needed, whereas 5-deiodination prevails when thyroid function needs to be suppressed.

The cardinal feature of ESS is the markedly depressed plasma concentration of total T3, resulting from a decrease in the conversion of T4 to T3 in the peripheral tissues, mediated by inhibition of 5'-deiodinase. The plasma concentration of total rT3 is increased reciprocally. The plasma concentration of total T4 is normal or low, whereas that of fT4 may be increased modestly from a defect in the binding of the thyroid hormone to its carrier proteins (TBG, transthyretin, and albumin). The plasma concentration of TSH may be low, reflecting immaturity of the hypothalamic-pituitary-thyroid axis.

Euthyroid sick syndrome has many causes, which include:

- systemic infection
- systemic illness resulting in hypoxemia, hypercapnea, and hypotension
- metabolic derangements such as hypoglycemia and hypocalcemia
- organ dysfunction including liver and kidney disease
- injury from trauma, surgery, and burns
- catabolic conditions such as malnutrition
- medications such as glucocorticosteroids and dopamine

The changes in thyroid function resulting from these factors probably are triggered by cytokines released from macrophages and monocytes as a part of a systemic immune response. The earliest evidence of thyroid dysfunction in systemic illness is the depletion of circulating T3—hence the term low T3 syndrome—and a reciprocal increase in circulating rT3 (Figure).

Figure: Sequential changes in thyroid function in euthyroid sick syndrome

Worsening of the systemic illness is characterized by an additional depletion of circulating T4, often referred to as low T3-T4 syndrome. Recovery from the systemic illness is characterized by reversal of these changes in thyroid function.
The preterm infant in this vignette has many of the factors that can contribute to ESS. Further research is needed to delineate the specific changes in thyroid function associated with ESS in preterm infants. This research may help determine whether thyroid hormone treatment is safe and efficacious in such cases.

References:


American Board of Pediatrics Content Specification(s):

Understand the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction

Understand the causes of transient hypothyroidism in the neonate

Understand the embryology and normal physiological function of the normal thyroid gland
A 28-year-old primiparous woman is about to deliver at an estimated gestational age of 34 weeks. Maternal history is significant for autoimmune thyrotoxicosis (Graves disease) diagnosed during the first trimester of pregnancy. Although propylthiouracil treatment was recommended, the mother's compliance with the medication has been poor. Evaluation of the thyroid status of the neonate is planned, specifically to determine the risk of neonatal thyrotoxicosis.

Of the following, the umbilical cord blood test MOST predictive of neonatal thyrotoxicosis is the measurement of:

- thyroid-stimulating hormone
- thyroxine-binding globulin
- total reverse triiodothyronine
- total tetraiodothyronine
- total triiodothyronine

You selected 2, the correct answer is 1.

Hyperthyroidism in the pregnant woman is uncommon with an estimated incidence of 1 to 2 cases per 1,000 pregnancies. The most common cause of maternal hyperthyroidism is autoimmune thyrotoxicosis (Graves disease), accounting for approximately 90% of cases. Hyperthyroidism in the neonate is rare, occurring only in about 1 in 70 pregnancies complicated by maternal thyrotoxicosis. The neonatal disease is attributed to transplacental passage of maternal thyroid-stimulating immunoglobulin (TSI). The titer and the rate of clearance of TSI determines the duration of the neonatal disease. A maternal TSI titer exceeding 500% of control reference values is associated with fetal and/or neonatal thyrotoxicosis. The half-life of maternal TSI in the newborn is approximately 21 days, which accounts for the typical duration of neonatal disease that varies between 3 and 12 weeks after birth.

Most antithyroid drugs, including propylthiouracil, readily cross the placenta and potentially can suppress thyroid function in the fetus/neonate. However, when maternal thyrotoxicosis is controlled judiciously with appropriate dosage of antithyroid drugs and careful monitoring of maternal thyroid status, the risk of fetal/neonatal hypothyroidism is low. Because the mother in this vignette was not compliant with antithyroid medication, her fetus/neonate is not likely to manifest hypothyroidism. On the contrary, the mother's uncontrolled thyrotoxicosis raises the likelihood of thyrotoxicosis in her fetus/neonate.
The umbilical cord blood test most predictive of neonatal thyrotoxicosis is the measurement of thyroid-stimulating hormone (TSH). The normal TSH in cord blood ranges from 3.0 to 12.0 mIU/mL. A TSH value less than 0.05 mIU/mL, indicating suppression of anterior pituitary in response to the hyperthyroid state, is diagnostic of neonatal thyrotoxicosis. In neonatal thyrotoxicosis, the cord blood concentrations of total tetraiodothyronine (thyroxine, T₄), triiodothyronine (T₃), and reverse triiodothyronine (rT₃) are usually normal.

The most striking physiologic increase in plasma concentration of thyroxine-binding globulin (TBG)—the principal thyroid hormone–binding protein—occurs during pregnancy. This increase is attributed primarily to an increase in sialic acid content, which prolongs the biological half-life of TBG. The increase in maternal plasma TBG concentration may be observed as early as 3 weeks after implantation and reaches its peak around the end of the second trimester and the beginning of the third trimester of pregnancy. In the newborn, the plasma TBG concentration is approximately 1.5 times the normal adult concentration of 1.0 to 2.0 mg/dL (160-320 nmol/L). The cord blood concentration of TBG is not predictive of neonatal thyrotoxicosis.

The clinical manifestations of neonatal thyrotoxicosis include irritability and tremors, tachycardia and hypertension, and poor weight gain or excessive weight loss. Thyroid enlargement and exophthalmos are invariably present. Hepatosplenomegaly with jaundice, thrombocytopenia, and hypoprothrombinemia have been observed. The symptoms and signs of neonatal thyrotoxicosis may be delayed as long as 8 to 10 days after birth. This delay often is the result of maternal antithyroid treatment, which may suppress the thyroid function in the neonate initially. Untreated, neonatal thyrotoxicosis has a 25% risk of mortality, which may result from cardiac arrhythmia and failure.

Do you want to add anything to your Learning Plan?
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References:

American Board of Pediatrics Content Specification(s):
Identify the etiology and clinical manifestations of congenital hyperthyroidism
Know the laboratory features and treatment of congenital hyperthyroidism
A 48-hour-old male infant, who weighed 3,400 g at birth at an estimated gestational age of 38 weeks, is lethargic, feeding poorly, and cold to the touch. The infant was born after an uncomplicated pregnancy and spontaneous vertex vaginal delivery. The Apgar scores were 8 and 9 at 1 and 5 minutes after birth, respectively; the umbilical cord arterial blood pH was 7.31.

Clinical examination reveals an appropriately grown infant with no dysmorphic features or evidence of physical injury. The vital signs are normal except for an increased spontaneous respiratory rate of 100 breaths per minute. Neurologic examination reveals obtundation consciousness, generalized hypotonia with paucity of movement, suppressed tendon reflexes, and normally reactive pupils. There are no indications of sepsis or meningitis based on maternal history, blood cell counts, inflammatory markers, or cerebrospinal fluid findings.

Laboratory data are as follows.

<table>
<thead>
<tr>
<th>Laboratory Findings</th>
<th>Patient Result (SI Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial blood gas measurements</strong></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.58</td>
</tr>
<tr>
<td>Partial pressure of carbon dioxide, mm Hg (kPa)</td>
<td>18 (2.3)</td>
</tr>
<tr>
<td>Partial pressure of oxygen, mm Hg (kPa)</td>
<td>80 (10.4)</td>
</tr>
<tr>
<td>Base deficit, mEq/L (mmol/L)</td>
<td>2.0 (2.0)</td>
</tr>
<tr>
<td><strong>Plasma measurements</strong></td>
<td></td>
</tr>
<tr>
<td>Ammonia, μmol/L</td>
<td>840 (normal 56-92)</td>
</tr>
<tr>
<td>Glucose, mg/dL (mmol/L)</td>
<td>84 (4.7) (normal 60-105 [3.3-5.8])</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>1.2 (normal 0-3.0)</td>
</tr>
<tr>
<td><strong>Urine measurements</strong></td>
<td></td>
</tr>
<tr>
<td>Ketones</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Chest radiography shows a normal heart outline and clear lung fields. Cranial ultrasonography shows moderate cerebral edema.

Of the following, the MOST likely inherited metabolic disease in this infant is:

1. fatty acid oxidation disorder
2. maple syrup urine disease
3. nonketotic hyperglycinemia
4. organic acidopathy
5. urea cycle disorder

You selected 3, the correct answer is 5.
Acute encephalopathy, as manifested by the infant in this vignette, is a presenting feature of a number of inherited metabolic diseases. The deterioration of consciousness resulting from an inherited metabolic disease typically occurs with little warning in a previously healthy appearing infant, progresses rapidly to stupor and coma, and is accompanied by no focal neurologic deficits. Delays in diagnosis and treatment can result in death or severe neurologic morbidity.

The markedly increased plasma ammonia concentration in the infant in this vignette is characteristic of a urea cycle disorder. Genetic defects in one of four enzymes of the urea cycle (carbamoyl phosphate synthase, ornithine transcarbamoylase, argininosuccinic acid synthase, and argininosuccinic acid lyase) or of the obligatory cofactor (N-acetyl glutamate synthase) result in accumulation of precursor metabolites including ammonia. Because there is no effective secondary clearance mechanism for ammonia, disruption of the urea pathway has a rapid clinical course. The catabolism normally present early after birth relative to the later neonatal period, coupled with the immaturity of the newborn liver, can accentuate the defects in these enzymes.

The rapid accumulation of ammonia results in acute cerebral edema with neurologic compromise. Seizures are seen in approximately 50% of severely hyperammonemic neonates. Hyperventilation induced by cerebral edema causes respiratory alkalosis, as in the infant in this vignette, in the early stages of hyperammonemia, which progresses to hypoventilation and respiratory arrest as pressure builds on the brainstem. Loss of thermoregulation with resultant fall in core body temperature is typical. In contrast to increased plasma ammonia concentration in the urea cycle disorder, the plasma concentrations of glucose and lactate typically are normal and the urine is normal for ketones (Table).

| Table. Inherited Metabolic Diseases Presenting as Acute Encephalopathy* |
|-----------------------------|-------------|-----------|-----------|-----------|
|                             | UCD        | FAOD      | MSUD      | NKHG      |
| Plasma ammonia              | ↑↑         | ↑         | N         | N         |
| Plasma glucose              | N          | ↓↓        | N or ↓    | ↑         |
| Plasma lactate              | N          | ±         | N         | ↑         |
| Metabolic acidosis          | O          | ±         | ±         | O         |
| Liver enzymes               | N          | ↑↑        | N         | N         |
| Urine ketones               | N          | O         | ↑↑↑       | N         |

* Adapted from Clarke [2002].

Abbreviations: UCD = urea cycle disorder; FAOD = fatty acid oxidation disorder; MSUD = maple syrup urine disease; NKHG = nonketotic hyperglycinemia; OAP = organic acidopathy; N = normal; O = absent; ± = variable.

Acute encephalopathy is a common presenting feature of a fatty acid oxidation disorder. The most common fatty acid oxidation disorder is medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. Affected children usually present in the first or the second year after birth with nonspecific symptoms including lethargy, often precipitated by an intercurrent illness. Lethargy can progress rapidly to stupor and coma. Sudden unexpected death from cardiac arrhythmia is common in infants with unrecognized MCAD deficiency. The distinctive biochemical features of a fatty acid oxidation disorder include nonketotic hypoglycemia and hepatocellular dysfunction (Table). The plasma concentration of ammonia is mildly or moderately increased. The plasma concentration of lactate is variable and so is the evidence for metabolic acidosis. The urine is negative for ketones.

Maple syrup urine disease (MSUD), an inherited metabolic disease caused by branched-chain α-ketoacid dehydrogenase deficiency, typically presents in the newborn period as an acute encephalopathy. Milder variants of the disease may present at any age during childhood. A distinctive clinical feature of MSUD is the odor that resembles the smell of burned sugar. The distinctive biochemical feature of MSUD is the presence of high concentrations of ketones in the urine (Table). Testing the urine for α-ketoacids by addition of dinitrophenylhydrazine reagent produces a strongly positive reaction. The plasma concentration of glucose may be
normal or low. The evidence for metabolic acidosis is variable. Quantitative analysis of plasma amino acids is the most rapid and reliable method to confirm the diagnosis. Marked increases in concentrations of leucine, isoleucine, and valine, and the presence of alloisoleucine are diagnostic of MSUD.

Nonketotic hyperglycinemia (NKHG), an inherited metabolic disease caused by a deficiency of hepatic glycine cleavage, is characterized by early onset, rapidly progressive encephalopathy with virtually no secondary biochemical abnormalities (Table). Quantitative analysis of plasma amino acids usually shows an increase in glycine concentration. This increase, however, may be only modest because of the urinary loss of glycine in the early neonatal period resulting from immature renal function. The demonstration of increased glycine concentration in the cerebrospinal fluid is consistent and specific for the diagnosis of NKHG.

Propionic acidemia, methylmalonic acidemia, and isovaleric acidemia are examples of organic acidopathies that may present in the newborn period as acute encephalopathy. The distinguishing biochemical feature of an organic acidopathy is metabolic acidosis (Table). The anion gap in the affected infants typically is increased (>25 mmol/L), and measurements of lactate, 3-hydroxy butyrate, and acetoacetate usually account for only a part of this increase. Identification of the unmeasured anion by urinary organic acid analysis is important for the diagnosis. The plasma concentrations of ammonia and lactate are mildly or moderately increased, whereas the plasma concentration of glucose is often low. The urine is positive for ketones. Many affected infants have hematologic abnormalities such as neutropenia and thrombocytopenia. Confirmation of the diagnosis requires analysis of the relevant enzyme activities in cultured skin fibroblasts, coupled in some cases with specific mutation analysis.

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References:


American Board of Pediatrics Content Specification(s):

- Recognize and diagnose the metabolic disorders that lead to coma
- Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids
- Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids
- Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of urea cycle
- Understand the clinical manifestations, laboratory features, and treatment of disorders of organic acids
A 2-day-old term newborn is being evaluated for ambiguous genitalia (Figure 1).

Figure 1: Ambiguous genitalia

The karyotype is 46,XX. The genital examination reveals moderate clitoral widening, posterior midline labial fusion, partially covered vaginal orifice, and a pin-hole–like urethral meatus at the base of the phallic structure. No gonads are palpable. Blood pressure is normal. The serum electrolytes are also normal. Ultrasonography of the pelvis shows the presence of ovaries and the uterus. Ultrasonography of the abdomen shows redundant coils of adrenal tissue indicative of marked adrenal enlargement (Figure 2, A and B).

Figure 2: Ultrasonographic image of adrenal gland

Biochemical studies for products of adrenal steroidogenesis are pending. The infant has no other anomalies or dysmorphic features, is breathing spontaneously in room air, and is receiving enteral feeds.

Of the following, the MOST likely cause of genital ambiguity in this infant is a deficiency of the
The clinical features in the infant in this vignette are consistent with partial masculinization of female genitalia. The ultrasonographic findings are suggestive of congenital adrenal hyperplasia (CAH). The most common cause of CAH is an enzymatic defect in adrenal steroidogenesis, which results in decreased cortisol production. Loss of negative feedback inhibition of the hypothalamic-pituitary-adrenal axis by cortisol induces oversecretion of adrenocorticotropic hormone by the anterior pituitary, which results in adrenal hyperplasia. The associated excess of androgenic steroid secretion by the adrenal gland masculinizes the female genitalia in the developing fetus.

To understand the disorder of CAH, it is important to review the normal enzymatic sequence involved in adrenal steroidogenesis (Figure 3).

**Figure 3: Pathways of adrenal steroidogenesis**

Cholesterol, the primary precursor of adrenal steroidogenesis, is processed along three pathways. The first pathway, processed largely in the outermost of three layers of the adrenal cortex, called *zona glomerulosa*, results in the formation of mineralocorticoids, principally aldosterone. Aldosterone is involved in salt-water homeostasis. The second pathway, processed largely in the middle of three layers of the adrenal cortex, called *zona fasciculata*, results in the formation of glucocorticoids, principally cortisol. Cortisol is involved in several homeostatic functions, including glucose balance and vascular integrity. The third pathway, processed largely in the innermost of three layers of the adrenal cortex, called *zona reticularis*, results in the formation of androgens. The androgens are involved in external genital morphogenesis.
Congenital adrenal hyperplasia is classified into two forms: a classic form characterized by a marked reduction in enzyme activity resulting in clinical manifestations at birth, and a nonclassic form characterized by a less severe enzymatic defect resulting in clinical manifestations that are delayed and generally milder. The classification of CAH into subtypes is based on the specific enzymatic defect.

The most common cause of classic CAH is 21-hydroxylase deficiency, accounting for 90% to 95% of cases. The enzyme 21-hydroxylase (CYP21, also termed P450c21) is a cytochrome P450 enzyme. The gene for the enzyme, CYP21, is located on chromosome 6p21.3. The enzyme catalyzes the conversion of progesterone to deoxycorticosterone, a precursor of aldosterone, and the conversion of 17-hydroxypregnenolone to 11-deoxycortisol, a precursor of cortisol (Figure 3). Classic 21-hydroxylase deficiency is detected in approximately 1 in 16,000 births in most populations. Approximately 75% of patients with classic 21-hydroxylase deficiency have a concurrent defect in aldosterone synthesis (salt-wasting type), and the remainder have relatively normal aldosterone synthesis (simple virilizing type).

Girls with classic 21-hydroxylase deficiency are exposed to high systemic concentrations of adrenal androgens from approximately the seventh week of gestation. The affected girls have ambiguous genitalia: a large clitoris, rugated and partially fused labia majora, and a common urogenital sinus in place of a separate urethra and vagina. The uterus, fallopian tubes, and ovaries are normally formed. In contrast, the affected boys have no overt signs of the disease except variable and subtle hyperpigmentation and penile enlargement. The diagnosis of 21-hydroxylase deficiency is confirmed by demonstration of markedly increased serum concentrations of 17-hydroxyprogesterone, often in excess of 10,000 ng/dL (300 nmol/L) (normal <100 ng/dL [3 nmol/L]). The serum concentrations of dehydroepiandrosterone and androstenedione are also elevated.

The second common cause of classic CAH is 11β-hydroxylase deficiency, accounting for 5% to 8% of cases. The enzyme 11β-hydroxylase (CYP11B, also termed P450c11) is a cytochrome P450 enzyme. The gene for the enzyme, CYP11B, is located on chromosome 8q24.3. The enzyme catalyzes the conversion of deoxycorticosterone to corticosterone, and the conversion of 11-deoxycortisol to cortisol (Figure 3). Classic 11β-hydroxylase deficiency is detected in approximately 1 in 100,000 births in most populations; the incidence is much higher and estimated at 1 in 5,000 to 1 in 7,000 births among Jewish families of North African origin.

Girls with classic 11β-hydroxylase deficiency are exposed to high systemic concentrations of adrenal androgens from approximately the seventh week of gestation. The affected girls have ambiguous genitalia: a large clitoris, rugated and partially fused labia majora, and a common urogenital sinus in place of a separate urethra and vagina. The uterus, fallopian tubes, and ovaries are normally formed. In contrast, the affected boys have no overt signs of the disease. Approximately two thirds of patients with 11β-hydroxylase deficiency manifest hypertension, attributed to deoxycorticosterone-induced sodium retention. The diagnosis of 11β-hydroxylase deficiency is confirmed by demonstration of markedly increased serum concentrations of deoxycorticosterone and 11-deoxycortisol, as well as their urinary tetrahydrometabolites.

A rare cause of classic CAH is 3β-hydroxysteroid dehydrogenase deficiency, accounting for fewer than 5% of cases. The enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD) is present not only in the adrenal cortex, gonads, and placenta, but also in the liver and most peripheral tissues. The gene for the adrenal/gonadal enzyme, HSD3B2, is located on chromosome 1p13.1. The enzyme catalyzes the conversion of inactive adrenal and gonadal steroids—pregnenolone, 17-hydroxypregnenolone, and dehydroepiandrosterone—to active hormones progesterone, 17-hydroxyprogesterone, and androstenedione (Figure 3).

Girls with classic 3β-HSD deficiency typically present with masculinization of external genitalia, analogous to patients with 21-hydroxylase deficiency. In contrast, the affected boys have no overt signs of the disease. Approximately two thirds of patients with 3β-hydroxylase deficiency manifest hypertension, attributed to deoxycorticosterone-induced sodium retention. The diagnosis of 3β-hydroxylase deficiency is confirmed by demonstration of markedly increased serum concentrations of deoxycorticosterone and 11-deoxycortisol, as well as their urinary tetrahydrometabolites.

Congenital adrenal hyperplasia from 17α-hydroxylase deficiency is extremely rare. The enzyme 17α-hydroxylase (CYP17, also termed P450c17) is a cytochrome P450 enzyme. The gene for the enzyme, CYP17, is located on chromosome 10q24.3. The enzyme catalyzes the conversion of mineralocorticoid precursors to glucocorticoid precursors (17α-hydroxylase activity), and the conversion of glucocorticoid precursors to androgenic steroids (17,20-lyase activity) (Figure 3).
In affected patients, excess mineralocorticoid activity accounts for hypernatremia (and related hypertension), hypokalemia, and metabolic alkalosis, whereas the sex development is typically unaffected. The diagnosis of 17α-hydroxylase deficiency is established by demonstration of markedly increased serum concentrations of corticosterone and 18-hydroxycorticosterone.

Congenital adrenal hyperplasia from cholesterol desmolase deficiency, also called lipoid CAH, is extremely rare. The enzyme cholesterol desmolase (CYP11A, also termed \textit{P450scc}) is a cytochrome P450 enzyme. Mutations leading to lipoid CAH occur in the gene coding for \textit{StAR} protein, \textit{StAR} gene, located on chromosome 8p11.2, or in the gene, \textit{CYP11A}, located on chromosome 15q23-24. The enzyme catalyzes the conversion of cholesterol to pregnenolone, the first and rate-limiting step in the production of all adrenal steroids (Figure 3). Massive accumulation of cholesterol in the adrenal cortical tissue leads to characteristic fatty appearance of the adrenal gland and hence the descriptive term for the disease. Affected patients manifest severe fluid and electrolyte disturbances, hyperpigmentation, susceptibility to infection, and hypogonadism. Most patients do not survive infancy. The diagnosis of cholesterol desmolase deficiency is established by demonstration of absence of all adrenal steroids in plasma or urine.

References:


American Board of Pediatrics Content Specification(s):

Understand the basic enzymatic defects involved in the various types of congenital adrenal hyperplasia

Recognize the clinical manifestations and laboratory features of the various types of congenital adrenal hyperplasia

Know the etiology and diagnosis of an infant with ambiguous genitalia, including congenital adrenal hyperplasia

Know the clinical manifestations and laboratory features of an infant with ambiguous genitalia, including congenital adrenal hyperplasia
A 4-month-old African-American infant is hospitalized in March for treatment of bronchiolitis. Physical examination reveals a well-grown, mildly dehydrated infant in moderate respiratory distress. No dysmorphic features or neurologic abnormalities are noted. Laboratory findings are as follows:

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Patient Result (SI Value)</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, mg/dL (mmol/L)</td>
<td>0.4 (35.4)</td>
<td>0.2-0.6 (17.7-53.1)</td>
</tr>
<tr>
<td>Calcium, mg/dL (mmol/L)</td>
<td>7.9 (1.97)</td>
<td>8.5-11 (2.21-2.74)</td>
</tr>
<tr>
<td>Phosphorus, mg/dL (mmol/L)</td>
<td>2.9 (0.93)</td>
<td>4-8.1 (1.29-2.61)</td>
</tr>
<tr>
<td>Albumin, g/dL (g/L)</td>
<td>3.4 (34)</td>
<td>3.5-5 (35-50)</td>
</tr>
<tr>
<td>Alkaline phosphatase, units/L</td>
<td>878</td>
<td>5-550</td>
</tr>
</tbody>
</table>

The infant's history includes delivery at 36 weeks' gestation and a 5-day stay in the nursery to establish feedings. Since his discharge from the hospital, he has been exclusively breastfed, with appropriate weight gain and attainment of developmental milestones. This respiratory infection is his first illness, and he has received no medications. Although a multivitamin with iron had been prescribed, his mother admits to noncompliance because she had only planned to breastfeed for 6 months. The infant's mother takes no medications or supplements, and lists lactose intolerance as her only medical condition. In addition, to avoid infectious exposures, the infant and her mother have largely stayed indoors since arriving home from the nursery.

Of the following, the MOST likely additional finding in this infant is decreased:

- renal tubular 1-alpha-hydroxylase activity
- serum 1,25-dihydroxycholecalciferol concentration
- serum parathyroid hormone concentration
- serum 25-hydroxycholecalciferol concentration
- urinary phosphorus excretion

You selected 2, the correct answer is 4.

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Based on the laboratory findings of hypocalcemia, hypophosphatemia, and elevated alkaline phosphatase concentration, and the history of exclusively breastfeeding without mineral or vitamin supplementation, the likely diagnosis for the infant in the vignette is biochemical rickets secondary to vitamin D deficiency. Additional risk factors for this infant include being dark-skinned, limited exposure to sunlight, and probable vitamin D insufficiency in the mother because of her lactose intolerance.

Vitamin D (cholecalciferol) is a prohormone that is essential for intestinal absorption of dietary calcium and phosphorus. In the vitamin...
D–sufficient state, net calcium absorption is approximately 30%, and can reach as high as 80% during periods of active growth. In a state of vitamin D deficiency, calcium absorption decreases to 10% to 15%. Bone mineralization is dependent on the availability of calcium and phosphorus, and their deficiency leads to rickets, or osteomalacia of immature bones and cartilage. In addition, emerging evidence supports a role for vitamin D in maintaining innate immunity, and preventing latent disease processes including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, and some forms of cancer.

The major circulating and storage form of vitamin D is 25-hydroxycholecalciferol (25[OH] vitamin D, calcidiol), derived from hydroxylation of ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃) in the liver. In the proximal renal tubule (and other sites such as alveolar macrophages, lymph nodes, colon, and osteoblasts), parathyroid hormone–stimulated 1-alpha-hydroxylase converts calcidiol to 1,25-dihydroxycholecalciferol (1,25[OH]₂ vitamin D, calcitriol), the biochemically active form of vitamin D.

Three sources contribute to the status of circulating vitamin D. In the neonate, maternal calcidiol transplacentally acquired by the fetus comprises the major source of vitamin D. However, because the half-life of calcidiol is 3 to 4 weeks, serum concentrations in the neonate fall rapidly after delivery. Postnatally, cutaneous vitamin D synthesis is an important source of this prohormone. In the lipid bilayer of the plasma membrane of epidermal keratinocytes and dermal fibroblasts, 7-dehydrocholesterol (provitamin D₃) exposed to UV-B in the wavelengths of 290 to 315 nm is converted to previtamin D₃, and then isomerized to vitamin D. Subsequently, vitamin D is protein bound and transported to the liver for hydroxylation.

Dietary vitamin D is the other important source of this prohormone. Vitamin D is absorbed in the small intestine by passive diffusion after solubilization by bile salts. Natural sources include oily fish such as salmon, cod liver oil, organ meats, liver, and egg yolk. Breast milk and cow's milk are insufficient sources of vitamin D. From a vitamin D–sufficient mother, the vitamin D content in breast milk averages approximately 22 international units/L (range, 15-50 international units/L). Likewise, unfortified cow's milk contains 3 to 40 international units/L of vitamin D. Exclusive breastfeeding, with an average consumption of 750 mL per day provides only 11 to 38 international units/ per day of vitamin D, which is far below the recommended minimum intake of 400 international units/day. In the United States, infant formulas are fortified to at least 400 international units/L of vitamin D, to ensure that with an intake of at least 500 mL per day, daily vitamin D requirements are met.

Vitamin D deficiency rickets, a major scourge of children during the industrial revolution, largely disappeared with the recognition of the roles of sunlight and vitamin D. In 1925, a landmark clinical trial demonstrated the beneficial effects of cod liver oil and regular sunlight exposure in reducing the incidence and severity of rickets. By the 1930s, vitamin D was regularly added to formulas derived from cow’s milk, and supplementation was provided to infants fed breast milk. But toward the end of the century, the reported incidence of nutritional rickets was on the rise again, purportedly an unintended consequence of the promotion of breast milk feeding and limiting sun exposure. Because melanin acts as a neutral filter and absorbs solar radiation, thereby interfering with cutaneous synthesis of vitamin D, infants who are dark-skinned and exclusively breastfed without vitamin D supplementation are at highest risk. Similarly, maternal vitamin D status is a major influence on the vitamin D content of human milk; dark-skinned mothers are themselves at high risk for vitamin D deficiency. Finally, vitamin D supplementation has been neither universally prescribed nor consistently given for exclusively breastfed infants.

Vitamin D deficiency can be described in three progressive stages, with a biochemical deficiency occurring months before obvious physical examination findings of rickets. In the first stage, impaired calcium absorption results in mild hypocalcemia and compensatory elevation of parathyroid hormone concentration that subsequently normalizes calcium concentration. Infants in this stage are typically asymptomatic and the transient hypocalcemia may be easily missed. In the next stage, secondary hyperparathyroidism results in hypophosphatemia, phosphaturia, elevation of 1,25(OH)₂ vitamin D and alkaline phosphatase concentrations, and increased calcium and phosphorus mobilization from the bone. Evidence of bone mineral loss and rachitic changes begin to be apparent on radiography and physical examination. Severely depressed calcium and phosphorus concentrations characterize the
third stage, and may result in tetany, seizures, cardiomyopathy, and death.

The most objective measure of vitamin D sufficiency is the concentration of 25(OH) vitamin D. The diagnosis of vitamin D deficiency rickets is supported by characteristic biochemical changes, along with a history of poor vitamin D intake. A low 25(OH) vitamin D concentration combined with hypophosphatemia and radiologic evidence of rickets is confirmatory. The concentration of 1,25(OH)₂ vitamin D is less useful. In states of profound vitamin D deficiency, the concentration of 1,25(OH)₂ vitamin D is usually low, but in moderate, classic nutritional rickets, parathyroid hormone–stimulated 1-alpha-hydroxylase can result in normal or elevated concentrations. Elevation of serum parathyroid hormone concentration occurs in all three stages. Alkaline phosphatase is an indicator of osteoclast activity and is often, but not invariably correlated with disease severity. However, alkaline phosphatase concentration is not specific to metabolic bone disease, as hepatobiliary disease states also result in elevated concentrations.

To prevent vitamin D deficiency in infants, children, and adolescents, and to maintain 25(OH) vitamin D concentrations at 50 nmol/L (20 ng/mL) or higher, the current recommended minimum intake of vitamin D is 400 international units per day (which is the amount contained in one teaspoon of cod liver oil). In 2008, the American Academy of Pediatrics (AAP) reiterated its recommendation for a vitamin D supplement of 400 international units per day for breastfed infants and nonbreastfed infants who consume less than 1 L or 1 qt per day of vitamin D–fortified formula. The updated AAP guideline supports beginning vitamin D supplementation during the first few days of age, and continuing throughout adolescence if dietary sources remain insufficient.

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References:


American Board of Pediatrics Content Specification(s):

Understand the requirements for vitamins in newborn infants and the difference between the preterm and the full-term infant

Understand the interrelated effects of various hormones, including parathormone, calcitonin, and vitamin D on calcium, phosphorus, and magnesium metabolism in the fetus and neonate

Understand the clinical and laboratory manifestations of deficiencies of fat soluble vitamins

Understand the mineral and vitamin content of infant formulas
A 48-hour-old male infant, who weighed 3,400 g at birth at an estimated gestational age of 38 weeks, is lethargic, feeding poorly, and cold to the touch. The infant was born after an uncomplicated pregnancy and spontaneous vertex vaginal delivery. The Apgar scores were 8 and 9 at 1 and 5 minutes after birth, respectively.

Clinical examination reveals an appropriately grown infant with no dysmorphic features or evidence of physical injury. The vital signs are normal except for an increased spontaneous respiratory rate of 100 breaths per minute. Neurologic examination reveals obtunded consciousness, generalized hypotonia with paucity of movement, suppressed tendon reflexes, and normally reactive pupils. There are no indications of sepsis or meningitis based on maternal history, blood cell counts, inflammatory markers, or cerebrospinal fluid findings.

Chest radiography shows a normal heart outline and clear lung fields. Cranial ultrasonography shows moderate cerebral edema.

Laboratory data are as follows: arterial pH, 7.58; partial pressure of carbon dioxide, 18 mm Hg (2.3 kPa); partial pressure of oxygen, 80 mm Hg (10.4 kPa); and base deficit 2.0 mEq/L (2.0 mmol/L). Plasma concentrations were as follows: ammonia, 840 μmol/L (normal 56-92 μmol/L); glucose, 84 mg/dL (4.7 mmol/L) (normal 60-105 mg/dL [3.3-5.8 mmol/L]); lactate, 1.2 mmol/L (normal 0-3.0 mmol/L); and anion gap, 8.0 mEq/L (8.0 mmol/L). Urinary ketones are absent; urinary orotic acid is elevated. Plasma amino acid measurements are displayed in the Table.

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Value (μmol/L)</th>
<th>Normal Range (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine</td>
<td>48</td>
<td>6-140</td>
</tr>
<tr>
<td>Citrulline</td>
<td>3</td>
<td>10-45</td>
</tr>
<tr>
<td>Glutamine</td>
<td>542</td>
<td>376-709</td>
</tr>
<tr>
<td>Glycine</td>
<td>436</td>
<td>232-740</td>
</tr>
<tr>
<td>Histidine</td>
<td>52</td>
<td>30-138</td>
</tr>
<tr>
<td>Leucine</td>
<td>83</td>
<td>48-160</td>
</tr>
<tr>
<td>Methionine</td>
<td>32</td>
<td>10-60</td>
</tr>
<tr>
<td>Ornithine</td>
<td>422</td>
<td>48-211</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>68</td>
<td>38-137</td>
</tr>
<tr>
<td>Serine</td>
<td>210</td>
<td>99-395</td>
</tr>
<tr>
<td>Threonine</td>
<td>168</td>
<td>90-329</td>
</tr>
<tr>
<td>Valine</td>
<td>110</td>
<td>86-190</td>
</tr>
</tbody>
</table>

Of the following, the MOST likely enzyme defect in this infant involves:

1. arginosuccinate lyase
2. arginosuccinate synthase
3. carbamoyl phosphate synthase
4. N-acetyl glutamate synthase
Acute encephalopathy, as manifested by the infant in this vignette, is a presenting feature of a number of inherited metabolic diseases. The markedly increased plasma ammonia concentration is characteristic of a urea cycle disorder. The plasma amino acid profile, characterized by markedly increased ornithine concentration and decreased citrulline concentration, and the presence of orotic acid in the urine are consistent with a defect in ornithine transcarbamoylase (OTC, also known as transcarbamylase) enzyme.

To understand the urea cycle disorders, it is important to review the normal enzymatic sequence of the urea cycle.

Formation of Ammonia and Aspartate

Urea is the major disposal form of amino groups derived from amino acids. The amino groups of most amino acids are funneled to glutamate (Figure 1).

Glutamate is partly oxidized to ammonia, a reaction catalyzed by glutamate dehydrogenase, and partly deaminated to aspartate, a reaction catalyzed by aspartate transaminase. Ammonia is largely mitochondrial in location, whereas aspartate is largely cytosolic.

Formation of Carbamoyl Phosphate

In the mitochondrion, ammonia is coupled with carbon dioxide to form carbamoyl phosphate, a reaction catalyzed by carbamoyl phosphate synthase (CPS) (Figure 2).
This reaction also requires an obligatory cofactor, N-acetyl glutamate, which is derived from glutamate and acetyl-CoA, a reaction catalyzed by N-acetyl glutamate synthase (NAGS).

Formation of Citrulline

In the mitochondrion, carbamoyl phosphate combines with ornithine to form citrulline, a reaction catalyzed by OTC.

Formation of Argininosuccinate

Citrulline diffuses out of the mitochondrion into the cytosol, where it combines with aspartate to form argininosuccinate, a reaction catalyzed by argininosuccinate synthase (ASS).

Formation of Arginine

Argininosuccinate is cleaved to yield arginine and fumarate, a reaction catalyzed by argininosuccinate lyase (ASL).

Formation of Ornithine and Urea

Arginine is cleaved to yield ornithine and urea, a reaction catalyzed by arginase (ARG). Ornithine is relocated from the cytosol to the mitochondrion, a reaction facilitated by ornithine translocase (OTL). The intramitochondrial ornithine takes part in the reaction to form citrulline as described before. The cytosolic urea diffuses from the liver and is transported in the blood to the kidneys, where it is filtered and excreted in the urine.

A quantitative plasma amino acid analysis can be used to diagnose the specific urea cycle disorder. An increase in the plasma concentrations of amino acids proximal to the enzymatic defect and a concomitant decrease in the plasma concentrations of amino acids distal to the enzymatic defect can help determine the specific enzyme deficiency. Molecular genetic evaluation, based on the knowledge of the genes for specific enzymes and their chromosomal locations and gene products, can be used for confirmation of the diagnosis.

Ornithine transcarbamoylase deficiency, the most common form of urea cycle disorders, is characterized by intramitochondrial accumulation of carbamoyl phosphate, a marked increase in plasma concentration of ornithine, and a marked decrease in plasma concentration of citrulline. The intramitochondrial carbamoyl phosphate diffuses into the cytosol and stimulates pyrimidine biosynthesis, which results in accumulation of orotic acid. The presence of increased concentrations of orotic acid in the urine distinguishes OTC deficiency from deficiencies of both CPS and NAGS. The gene for the enzyme OTC is located on chromosome...
Xp21.1, which accounts for the X-linked inheritance of OTC deficiency.

Carbamoyl phosphate synthase deficiency, the most severe form of urea cycle disorders, is characterized by intramitochondrial depletion of carbamoyl phosphate, a marked increase in plasma concentration of ornithine, and a marked decrease in plasma concentration of citrulline. The urine is negative for orotic acid. The gene for the enzyme CPS is located on chromosome 2q35; the mode of inheritance of CPS deficiency is autosomal recessive.

N-acetyl glutamate synthase deficiency, a rare form of urea cycle disorders, is indistinguishable from CPS deficiency with regard to intramitochondrial carbamoyl phosphate and plasma amino acid changes. The urine is negative for orotic acid. The gene for the enzyme NAGS is located on chromosome 17q21.3; the mode of inheritance of NAGS deficiency is autosomal recessive.

Argininosuccinate synthase deficiency is characterized by a marked increase in plasma concentration of citrulline and a modest decrease in plasma concentration of arginine. In addition to its role in the urea cycle, ASS is involved in the cycling of arginine and citrulline in the production of nitric oxide. ASS deficiency, therefore, manifests in disorders related to nitric oxide such as pulmonary hypertension of the newborn. The gene for the enzyme ASS is located on chromosome 9q34; the mode of inheritance of ASS deficiency is autosomal recessive.

Argininosuccinate lyase deficiency is characterized by a modest increase in plasma concentration of citrulline and a marked decrease in plasma concentration of arginine. Like ASS, the enzyme ASL is involved in the cycling of arginine and citrulline in the production of nitric oxide. ASL deficiency, therefore, manifests in disorders related to nitric oxide such as pulmonary hypertension of the newborn. The gene for the enzyme ASL is located on chromosome 7 cen-q11.2; the mode of inheritance of ASL deficiency is autosomal recessive.

References:


American Board of Pediatrics Content Specification(s):

Recognize and diagnose the metabolic disorders that lead to coma

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle
A 2.6-kg full-term female infant was born through vaginal delivery to a 23-year-old woman after spontaneous onset of labor. One hour after birth, the infant’s blood glucose after breastfeeding was 28 mg/dL (1.6 mmol/L) which improved to 54 mg/dL (3 mmol/L), but fell again to 36 mg/dL (2 mmol/L). A glucose infusion was initiated and gradually weaned over the next 72 hours; oral feedings continued without recurrence of hypoglycemia but she was noted to feed poorly during the next several weeks.

In addition to transient hypoglycemia, hyperbilirubinemia was noted on the second day after birth. The bilirubin concentration rose to 21.3 mg/dL (364 μmol/L) by the 13th day with a conjugated fraction of 3.3 mg/dL (56 μmol/L) (Figure).

She was treated intermittently with phototherapy. Her hemoglobin concentration was 16 g/dL (160 g/L); direct Coombs test result was negative; red cell indices and morphology and urinalysis findings were normal. Aminotransferase enzymes, alkaline phosphatase, 5’ nucleotidase, total protein, and albumin concentrations were normal. Ultrasonography of the abdomen revealed a normal gall bladder. Findings of the first newborn screening conducted 30 hours after birth for metabolic, genetic, and endocrine diseases, including cystic fibrosis, were normal. Screening repeated 10 days later showed a below-normal thyroxin concentration.

Of the following, the MOST likely diagnosis explaining the findings in this infant is:

1. biliary atresia
2. Crigler-Najjar syndrome
3. Dubin-Johnson syndrome
4. hypothyroidism
You selected 4, the correct answer is 5.

The infant in the vignette has neonatal panhypopituitarism which should be suspected in newborn infants with significant hypoglycemia, feeding problems, and any of the following associated findings: micropenis, midline defects (eg, bifid uvula), blindness, eye abnormalities (eg, septo-optic dysplasia), or cholestatic jaundice. Unfortunately, infants with panhypopituitarism may have no characteristic findings at birth other than hypoglycemia. The infant in the vignette had hypoglycemia requiring treatment, feeding problems, and cholestatic jaundice.

Hormone deficiencies in infants with panhypopituitarism are important contributors to hypoglycemia. Hypoglycemia is mainly a consequence of deficient secretion of growth hormone and cortisol (glucocorticoid). Growth hormone and glucocorticoids promote gluconeogenesis, raising blood glucose concentrations. In addition, growth hormone suppresses the uptake of glucose by the liver while glucocorticoids promote hepatic glycogenolysis. Hypoglycemia is not a common consequence of isolated thyroid hormone deficiency.

Hypothyroidism does cause persistent and sometimes severe unconjugated hyperbilirubinemia. Therefore, the rise in the unconjugated fraction of bilirubin described in the infant in the vignette can be attributed to thyroid dysfunction. The liver enzyme that conjugates bilirubin, uridine 5'-diphospho-glucuronyltransferase 1A1 (UGT1A1), also conjugates thyroxin (T₄). As part of a feedback loop, T₄ stimulates the production of UGT1A1, explaining how thyroxin deficiency can result in unconjugated hyperbilirubinemia.

Crigler-Najjar syndrome is caused by a mutation in the UGT1A1 gene on chromosome 2q37 and results in an inactive enzyme. Infants with Crigler-Najjar syndrome gradually develop severe unconjugated hyperbilirubinemia with no measurable conjugated bilirubin.

The infant in the vignette had high conjugated bilirubin values in addition to elevated concentrations of unconjugated bilirubin. Once bilirubin is conjugated in the hepatocyte, it becomes a water-soluble molecule unable to diffuse through cell membranes. Conjugated bilirubin is excreted into the biliary tree using an energy-dependent membrane transporter called the canalicular multispecific organic anion transporter (cMOAT). This particular transporter has been described independently in various systems and is alternatively called the multidrug resistance–associated protein 2 (MRP2) or adenosine triphosphate–binding cassette C2 (ABCC2). It expels various water-soluble molecules across the cell membrane ranging from conjugated bilirubin to cancer chemotherapeutic agents. The gene is found on chromosome 10q24.

Dubin-Johnson syndrome (DJS) is caused by a genetic mutation of cMOAT and is characterized by lifelong mild to moderate conjugated hyperbilirubinemia. In DJS, conjugated bilirubin is produced but is not transported into bile. Instead, conjugated bilirubin accumulates in liver cells and appears in circulating plasma. DJS does not cause hypoglycemia and characteristically leads to mild cholestatic jaundice, often first noticed later in life.

The concentration of cMOAT in liver cell membranes is hormonally regulated. Hypophysectomized animals have little or no measurable cMOAT. Growth hormone partially restores liver cell membrane concentrations of cMOAT in hypophysectomized animals. Thyroxin does not increase concentrations of cMOAT by itself, but potentiates the effect of growth hormone, bringing concentrations to the normal range. Estrogen independently increases the production of cMOAT. Consequently, infants with panhypopituitarism often have an associated deficiency in cMOAT related to deficiencies in growth hormone, thyroxin, and estrogen.

Infants with biliary atresia usually have increased serum concentrations of biliary tree–related enzymes such as alkaline phosphatase and 5′ nucleotidase as well as increased concentrations of conjugated bilirubin. The rise in conjugated bilirubin usually appears...
following the first week after birth. In most cases, the gall bladder is not visualized with abdominal ultrasonography. Hypoglycemia is not a feature of biliary atresia.

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(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


American Board of Pediatrics Content Specification(s):

Recognize the etiology and clinical manifestations of neonatal hypoglycemia

Understand the clinical and laboratory manifestations of extrahepatic biliary atresia that differentiate it from neonatal hepatitis and other causes of cholestasis in the neonate

Understand the differential diagnosis, evaluation, and approach to management of mixed forms of jaundice
A 29-year-old woman who is 31 weeks' pregnant is admitted for nausea, vomiting, right upper quadrant pain, jaundice, and obtundation. Her blood pressure is elevated. Laboratory studies indicate thrombocytopenia (platelet count of $85 \times 10^3/\mu L$ [$85 \times 10^9/L$]), elevated concentrations of serum transaminases and ammonia, mildly prolonged prothrombin time, and hypoglycemia. Viral causes for liver dysfunction are excluded. Liver biopsy specimen shows microvesicular fatty infiltration. The woman had a child who had died of sudden infant death syndrome.

Of the following, the MOST likely fetal/neonatal diagnosis associated with this mother's condition is:

1. carnitine-acylcarnitine translocase deficiency
2. carnitine transporter deficiency
3. electron transport flavoprotein-alpha deficiency
4. long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
5. very-long-chain acyl CoA dehydrogenase deficiency

You selected 2, the correct answer is 4.
The fetus in the vignette is most likely to have long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency. Mothers who have acute fatty liver of pregnancy (AFLP), like the woman in the vignette, have a 1 in 5 chance of delivering an infant with LCHAD deficiency.

Acute fatty liver of pregnancy affects about 1 in 13,000 deliveries, usually between 30 and 38 weeks of gestation. No ethnic or pregnancy features are particularly prevalent and the condition can recur. Initial presenting signs are nonspecific. Nausea and vomiting (70% of cases) and right upper quadrant or epigastric pain (50%-80% of cases) are common. Other problems early in the course include jaundice, upper gastrointestinal hemorrhage, renal failure, infection, pancreatitis, and hypoglycemia. Hepatic encephalopathy occurs later. Recovery begins after delivery of the fetus, and is usually complete within a month. Although the diagnosis is clinically determined in most cases, liver biopsy is confirmatory. Radiographic studies are not diagnostic. Exclusion of other causes of liver failure, especially viral hepatitis and the HELLP (hemolysis, elevated liver function tests, and low platelets) syndrome is important to determine treatment. The presence of jaundice, hypoglycemia, and elevated prothrombin time tends to differentiate symptoms of AFLP from the HELLP syndrome.

The association of AFLP in mothers heterozygous for LCHAD and LCHAD deficiency in offspring is well established. About 60% of mothers carrying fetuses with LCHAD deficiency will develop AFLP, HELLP syndrome, or preeclampsia. The presence of the G1528C mutation in exon 15 of the alpha subunit of the 3-hydroxyacyl-CoA dehydrogenase enzyme (chromosome 2p23) of the fetus predisposes the mother to AFLP when the infant is homozygous for the G1528C mutation or is a compound heterozygote. Case studies have reported offspring with deficiencies of carnitine palmitoyl transferase I (CPT1), short-chain acyl-CoA dehydrogenase (SCAD), and medium-chain acyl-CoA dehydrogenase (MCAD); and maternal AFLP, HELLP syndrome, or preeclampsia.

The mechanism of maternal liver disease is unclear in LCHAD deficiency. The affected fetus is a primary source of hepatotoxic metabolites (Figure 1).

Figure 1: Proposed mechanism for fatty liver of pregnancy, HELLP (hemolysis, elevated liver function tests, and low platelets) syndrome, and preeclampsia. The four sources of hepatotoxic metabolites that may lead to these disorders are depicted.
The mother who is heterozygous for the G1528C mutation has reduced capacity to oxidize long-chain fatty acids and is a second source for hepatotoxic metabolites. Recently, animal studies have highlighted the placenta as another source of toxic fatty acid metabolites when genes encoding for key fatty acid oxidation enzymes are ablated. In addition, lipolysis is increased and beta-oxidation is decreased during pregnancy, thereby providing a fourth source of toxic fatty acid oxidation byproducts.

Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency is an autosomal recessive disorder of fatty acid oxidation that interrupts the sequential removal of 2-carbon acetyl-CoA units that fuel ongoing beta-oxidation, ketogenesis, steroid genesis, and the tricarboxylic acid cycle. The tricarboxylic acid cycle, or Kreb cycle, produces the reduced forms of nicotinamide adenine dinucleotide and flavin adenine dinucleotide to fuel the electron transport chain for adenosine triphosphate, or energy, production. Fatty acids constitute the largest energy reserve in the body; oxidation of fatty acids becomes important during fasting and stress and is a primary source of energy for the heart, liver, and skeletal muscles (Figure 2).

Figure 2: Mitochondria, fatty acid B-oxidation, tricarboxylic acid cycle, and electron transport chain. The figure depicts a cell with key enzymes for fatty acid oxidation within the plasma, outer
mitochondrial, and inner mitochondrial membranes. The carnitine/acylcarnitine shuttle, mitochondrial trifunctional protein (MTP) with component enzymes (including the 3-hydroxyacyl CoA dehydrogenase that is abnormal in the long-chain hydroxyacyl CoA dehydrogenase deficiency, or LCHAD) important for fatty acid oxidation, and enzyme deficiencies presented in the question and critique are depicted.

Ketone bodies (acetoacetate, beta-hydroxybutarate, acetone) are produced from acetyl CoA in hepatocytes during fatty acid oxidation; thus, when fatty acid oxidation is impaired, the concentration of ketones is lower than normal. In contrast, during fasting, dehydration (inborn errors of organic acid metabolism), or when glucose supply is limited (glycogen storage disease type 1) or uptake is impaired (congenital diabetes), excessive fatty acid oxidation may cause high concentrations of ketoacids and metabolic acidosis.
The last three reactions in fatty acid beta-oxidation are mediated by an enzyme complex called the mitochondrial trifunctional protein complex (MTP; Figure 2). The enzymes enoyl-CoA hydratase, 3-hydroxyacyl CoA dehydrogenase, and 3-ketoacyl-CoA thiolase are composed of four alpha and four beta units on the inner mitochondrial membrane. LCHAD is caused by an isolated deficiency of 3-hydroxyacyl CoA dehydrogenase that presents with signs of liver dysfunction in 80% of cases. The G1528C mutation is the cause of isolated deficiency of 3-hydroxyacyl CoA dehydrogenase and a primary factor for maternal liver disease. LCHAD, in 20% of cases, is caused by complete MTP deficiency and presents with cardiomyopathy or neuromuscular dysfunction. Maternal liver disease does not accompany complete MTP deficiency.

Infants with LCHAD present within hours to months after birth, often with prematurity, intrauterine growth restriction, nonketotic hypoglycemia, metabolic acidosis, hyperammonemia, hypotonia, and hepatic encephalopathy. Coma, cardiomyopathy, peripheral neuropathy, skeletal myopathy, retinopathy, or sudden unexpected death (accounting for 5%-8% of cases labeled as sudden infant death syndrome) also can be presenting findings or may develop later. Late episodic symptoms of myopathy, neuropathy, and retinopathy can be seen. Laboratory findings include normal to decreased free carnitine, increased acyl-to-free carnitine, increased free fatty acids, and increased C<sub>16</sub>-OH and C<sub>18</sub>-OH carnitines. Tandem mass spectrometry used in newborn screening programs can identify infants with LCHAD.

Fatty acid oxidation disorders (FAODs) are common causes of severe metabolic disease in newborns and infants. FAODs are recessively inherited. The incidences vary between 1 in 8,000 and 1 in 100,000 individuals. Most FAODs other than LCHAD and perhaps CPT1, SCAD, and MCAD are not associated with maternal liver disease. Examples include:

- Carnitine translocase deficiency. Neonatal presentation is common. Presenting findings include chronic, progressive liver failure, persistent hyperammonemia, and hypertrophic cardiomyopathy. Laboratory abnormalities include normal-to-low free carnitine and an abnormal acylcarnitine profile.

- Carnitine transporter deficiency. Neonatal presentation is uncommon. Presenting findings include cardiomyopathy, skeletal myopathy, liver disease, sudden death, and endocardial fibroelastosis. Laboratory abnormalities include low total and free carnitine and normal acylcarnitines, acylglycine, and organic acids.

- Electron transport flavoprotein-alpha deficiency (glutaric academia type II). Neonatal presentation is common. Presenting findings include fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy, and skeletal myopathy. Laboratory abnormalities include normal-to-low free carnitine; increased acyl-to-free carnitine ratio; and increased acylcarnitine, urine organic acid, and acylglycines.

- Very long-chain acyl CoA dehydrogenase deficiency. Neonatal presentation is common.
Presenting findings include dilated cardiomyopathy, arrhythmias, hypoglycemia, hepatic steatosis, late onset of stress-induced rhabdomyolysis, and episodic myopathy. Laboratory abnormalities include normal-to-decreased free carnitine, increased plasma C14.1 acylcarnitine, and increased plasma free fatty acids.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


Shekhawat PS, Matern D, Strauss AW. Fetal fatty acid oxidation disorders, their effect on maternal health and neonatal outcome: impact of expanded newborn screening on their diagnosis and management. Pediatr Res. 2005;57(5Part2):78R-86R


American Board of Pediatrics Content Specification(s):

Understand the clinical manifestations, laboratory features, and treatment of disorders of metabolism of fatty acids

Know the effects on the fetus of severe preeclampsia, including HELLP syndrome, its management

Understand the effects on the fetus of maternal metabolic disorders (other than diabetes mellitus) and their management

Understand the etiology, clinical manifestations, laboratory features, treatment, and management of infants with lysosomal and peroxisomal, and mitochondrial disorders

Recognize the metabolic disorders that lead to coma

Know the role of the placenta in energy metabolism of the fetus, including transfer of glucose, electrolytes, and amino acids to the fetus
A 7-day-old female neonate, whose birthweight was 3,400 g at an estimated gestational age of 38 weeks, has evidence of congenital hypothyroidism on newborn screening. Confirmatory laboratory tests of thyroid function reveal the following plasma concentrations.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroxine, total, µg/dL (nmol/L)</td>
<td>1.9 (25)</td>
<td>8.0-16.0 (103-206)</td>
</tr>
<tr>
<td>Thyroxine, free, ng/dL (pmol/L)</td>
<td>0.6 (8)</td>
<td>2.0-4.0 (27-54)</td>
</tr>
<tr>
<td>Triiodothyronine, total, ng/dL (nmol/L)</td>
<td>32 (0.5)</td>
<td>80-200 (1.2-3.1)</td>
</tr>
<tr>
<td>Triiodothyronine, free, pg/mL (pmol/L)</td>
<td>1.2 (1.9)</td>
<td>3.0-7.0 (4.6-10.8)</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, µU/mL (mU/L)</td>
<td>64 (64)</td>
<td>0.5-5.0 (0.5-5.0)</td>
</tr>
</tbody>
</table>

Of the following, the MOST likely cause of congenital hypothyroidism in this infant is:

1. central hypothyroidism
2. thyroid dysgenesis
3. thyroid dyshormonogenesis
4. thyroid hormone resistance
5. transient congenital hypothyroidism

You selected 3, the correct answer is 2.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The infant in this vignette has low plasma concentrations of total and free thyroid hormones and a high plasma concentration of thyroid-stimulating hormone (TSH), which are characteristic of congenital hypothyroidism. Congenital hypothyroidism is the leading cause of preventable mental retardation, with an incidence of approximately 1 in 4,000 live births. Newborn screening for congenital hypothyroidism and early replacement of thyroid hormone have led to dramatic improvements in neurodevelopmental outcome of affected infants.

The most common cause of congenital hypothyroidism is thyroid dysgenesis, which accounts for approximately 80% of cases. To understand thyroid dysgenesis, it is important to review embryonic thyroid development (Figure 1).

Figure 1: Thyroid anlage and first pharyngeal pouch of the embryo (from http://www.thyroidmanager.org/Chapter21/figures/figure17.png)
The thyroid gland originates from the foregut, a thyroid anlage becoming first visible by human embryonic day 20 to 22 as a midline endodermal thickening in the ventral wall of the primitive pharynx caudal to the first branchial arch. The thyroid anlage projects into the surrounding mesenchyme by embryonic day 24 and forms a thyroid bud, a diverticulum with endodermal lining. By embryonic day 30 to 40, the thyroid bud expands into a thyroid primordium. The thyroid primordium migrates caudally into the mesenchyme as it descends toward its final location. At this stage, the thyroid primordium is still connected to the floor of the pharynx by a narrow channel, the thyroglossal duct. The thyroglossal duct gradually regresses, and by embryonic day 60 to 70, the thyroid primordium loses all connections with the floor of the pharynx. The subsequent development is characterized by formation of thyroid lobes, expansion of the lobes with thyroid follicles, and differentiation of the thyroid primordium into a functional thyroid gland.

Thyroid dysgenesis represents an anomalous development of the embryonic thyroid gland. It manifests as a maldescended thyroid (ectopic thyroid), a normally located but partly developed thyroid (hypoplastic thyroid), or an absent thyroid (athyreosis). Thyroid dysgenesis usually presents as an isolated anomaly, but rarely can be associated with other malformations or syndromes. Among malformations, cardiac malformations represent the most frequent birth defects associated with thyroid dysgenesis. The syndromes associated with thyroid dysgenesis include Bamforth-Lazarus syndrome (mutation of FOXE1 gene, locus 9q22) and Williams syndrome (mutation of ELN gene, locus 7q11-23). Most cases of ectopic thyroid are sporadic in occurrence and show a female predominance. Most cases of hypoplastic thyroid and athyreosis are autosomal recessive in inheritance and occur equally in both sexes.

The second common cause of congenital hypothyroidism is thyroid dyshormonogenesis, which accounts for approximately 10% of cases and has an estimated incidence of 1 in 40,000 live births. To understand thyroid dyshormonogenesis, it is important to review the synthesis of thyroid hormones, which involves three critical steps: uptake of iodide, iodination of tyrosine, and deiodination of thyronines. The thyroid uptake of iodide from the circulating pool of iodide is under the influence of TSH. The iodination of tyrosine involves incorporation of iodine in specific positions within the tyrosyl ring of thyroglobulin, a glycoprotein synthesized by the endoplasmic reticulum of the thyroid follicle cells. This iodination of tyrosine is catalyzed by the enzyme thyroid peroxidase. The resultant iodotyrosines are moniodotyrosine (3-iodotyrosine) (Figure 2) and diiodotyrosine (3,5-diiodotyrosine) (Figure 3).

Figure 2: Monoiodotyrosine
These iodotyrosines have no hormonal activity. Coupling of the iodotyrosines, under the influence of thyroid peroxidase, results in the formation of iodothyronines. Each iodothyronine has two rings, an inner tyrosyl ring with positions designated as 3 and 5, and an outer phenolic ring with positions designated as 3′ and 5′. Tetraiodothyronine (3,3′,5,5′-tetraiodothyronine) (thyroxine, T₄) (Figure 4) is the principal product of thyroid hormone synthesis.

It has minimal biologic activity and acts mainly as a precursor of active thyroid hormone. Removal of iodine (deiodination) from specific positions within the tyrosyl and phenolic rings of T₄, under the influence of deiodinase, is required for the formation of functional thyroid hormone. Triiodothyronine (3,3′,5-triiodothyronine) (T₃) (Figure 5) is derived by 5′-deiodination; it is the most biologically active form of thyroid hormone.
Thyroid dyshormonogenesis represents a genetic mutation that affects the uptake of iodide, iodination of tyrosine, or deiodination of thyronines in the synthesis of the thyroid hormones. The affected infants typically have normally located and shaped thyroid glands that are enlarged as a result of TSH hyperstimulation, a compensatory response to the hypothyroid status. One of the common hereditary disorders of thyroid dyshormonogenesis is Pendred syndrome. This syndrome (mutation of PDS gene, locus 7q31) is an autosomal recessive disorder characterized by developmental abnormalities of the cochlea with resultant sensorineural hearing loss and diffuse thyroid enlargement from a defect in iodide uptake.

Central hypothyroidism accounts for approximately 5% of cases of congenital hypothyroidism, and has an estimated incidence of 1 in 100,000 live births. Central hypothyroidism, in contrast to thyroid dysgenesis and thyroid dyshormonogenesis (intrinsic thyroid abnormalities causing primary hypothyroidism), results from either pituitary underproduction of TSH (secondary hypothyroidism) or hypothalamic dysfunction involving thyrotropin-releasing hormone (tertiary hypothyroidism). An example of secondary congenital hypothyroidism is a rare condition of isolated familial TSH deficiency. This disorder is caused by mutations in the TSH \(\beta\) subunit gene on chromosome 1, which renders TSH nonfunctional. An example of tertiary congenital hypothyroidism is a rare condition of septo-optic dysplasia. This disorder is characterized by anomalies of the midbrain that cause abnormal hypothalamic and/or pituitary function, agenesis of septum pellucidum, and eye defects such as hypoplasia of optic nerves, chiasma, and infundibulum. In addition to hypothyroidism, the affected infants have deficiencies of growth hormone, adrenocorticotropic hormone, antidiuretic hormone, and gonadotropins.

Thyroid hormone resistance accounts for fewer than 5% of cases of congenital hypothyroidism, and has an estimated incidence of 1 in 100,000 live births. Infants with thyroid hormone resistance have clinical manifestations of hypothyroidism despite high plasma concentrations of \(T_4\) and \(T_3\) with normal or high plasma concentrations of TSH. Abnormalities in transmembrane transporters of thyroid hormones (mutation of MCT8 gene, locus Xq13.2) or in intracellular deiodinating enzymes in peripheral tissues account for the thyroid hormone resistance.

Transient congenital hypothyroidism accounts for 5% to 10% of cases of congenital hypothyroidism, and has an estimated incidence of 1 in 40,000 live births. Causes of transient congenital hypothyroidism include fetal exposure to antithyroid drugs (methimazole, propylthiouracil), transplacental acquisition of TSH receptor–blocking antibodies from mothers with autoimmune thyroid disease, or maternal ingestion of inadequate or excessive iodide. The clinical course is transient, varying in duration from 1 week to 4 months.

References:


American Board of Pediatrics Content Specification(s):

Understand the causes of transient hypothyroidism in the neonate

Know the etiology and clinical manifestations of congenital hypothyroidism

Know the laboratory features and approach to therapy of congenital hypothyroidism
February

ASSESSMENT PROGRESS: Total Questions: 10 Questions Answered: 5 Correct Answers: 1

Question 5

A 3-day old, 3,200-g vigorous and healthy-appearing term infant delivered to a 39-year-old mother. He is on your service pending maternal recovery from postpartum complications of cesarean delivery. Chorionic villus sampling at 9 weeks was 46,XY. His neonatal physical examination findings are normal. The child and mother will return to their home in a remote rural area of your state after discharge. You receive notification that the newborn screen for hypothyroidism is positive and you confirm the diagnosis. Thyroid hormone treatment is begun and follow-up plans are made with the endocrinology department.

Of the following, the risk of having associated congenital anomalies among infants with congenital hypothyroidism compared with normal infants is MOST increased in the:

- A. cardiovascular system
- B. gastrointestinal system
- C. genital system
- D. renal system
- E. skeletal system

Correct Answer: A

Congenital hypothyroidism (CH) is the most common of the congenital endocrine disorders, affecting 1 in 3,000 to 4,000 newborns. An overall risk for congenital anomalies of approximately 7% has been noted among children with CH compared with about 2% in the general population, with the greatest increased risk being for cardiovascular anomalies (Table 1). Of note, no increase in genital anomalies is noted.

Table 1: Risk for Anomalies Associated with Congenital Hypothyroidism*

<table>
<thead>
<tr>
<th>System</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>27.5</td>
<td>23.3-32.4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>8.3</td>
<td>5.7-11.9</td>
</tr>
</tbody>
</table>

*Table 1
Ninety-eight percent of CH cases arise sporadically. The thyroid gland is the first glandular tissue to be identified in the developing fetus, arising at 16 to 17 days’ gestation from two median anlagen, coming from the floor of the pharynx between the first and second branchial arches (forming follicular cells, secreting thyroid hormone), and from two lateral anlagen that arise as caudal projections of the fourth or fifth pharyngeal pouches (forming C cells, secreting calcitonin, and also some follicular cells). The follicular cells begin to trap iodide and secrete thyroid hormones by 10 to 12 weeks’ gestation.

Congenital hypothyroidism in its most common sporadic form is the result of thyroid gland dysgenesis (85%) arising from dysfunction of genes located at 14q31 involving the thyroid-stimulating hormone (TSH) receptor. Dysgenesis manifests as agenesis (40%), failure of descent (40%), or hypoplasia of a eutopic gland. Thyroid gland dysgenesis also may accompany syndromic CH, resulting from gene dysfunctions of transcription factors TITF-1, TITF-2, and PAX-8, and of the Gsα portion of the stimulatory G protein which participates in signal transduction across cell membranes. Some of these genes are active in other tissues; for instance, PAX-8 is active in normal urinary tract development, suggesting a relationship between thyroid and renal development.

Dyshormonogenesis results from defects in the metabolic steps leading from monoiiodotyrosine to the hormonally active iodothyronines (thyroxine and triiodothyronine) and accounts for about 15% of CH. Mutations in the genes associated with these metabolic steps commonly are autosomal recessive and clinically manifest as CH associated with goiter.

Infants confirmed as having CH after positive screening require thyroid supplementation and referral to an endocrinologist. Epidemiologic studies have regularly demonstrated increases in associated congenital anomalies with CH.

The composite odds ratio (OR) for cardiovascular disease of 27.5 suggests the need for careful cardiovascular examination and follow-up. In the vignette, genetic testing ruled out aneuploidy, which accounts for some of the overall cardiac morbidity in CH. Depending on whether prenatal ultrasonography included detailed evaluation of cardiac anatomy, echocardiographic evaluation may be useful for the family in the vignette as they are remote from care at a medical center. Cardiovascular anomalies in infants with CH are summarized in Table 2.

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Prevalence in CH Rate per 10,000 births</th>
<th>Comparison with non-CH infants Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardial cushion defect</td>
<td>275.5</td>
<td>91.4</td>
<td>62.1-134.5</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>183.7</td>
<td>40.7</td>
<td>25.4-64.9</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>622</td>
<td>22.8</td>
<td>17.6-29.6</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>81.6</td>
<td>20.1</td>
<td>9.9-40.3</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>602</td>
<td>17.4</td>
<td>13.4-22.7</td>
</tr>
</tbody>
</table>

* Adapted from Kumar and associates (2009).

Although the prevalence of skeletal anomalies is relatively low in both CH and non-CH populations, there is significant added risk for patients with CH (OR, 13.8; 95% CI, 7.8-24.4) (Table 3).

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Prevalence in CH Rate per 10,000 births</th>
<th>Comparison with non-CH infants Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>13.2</td>
<td>10.6-16.5</td>
<td></td>
</tr>
<tr>
<td>Skeletal</td>
<td>13.8</td>
<td>7.8-24.4</td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from Kumar and associates (2009).
Table 4: Renal Anomalies in Congenital Hypothyroidism (CH)*

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Prevalence in CH</th>
<th>Comparison with non-CH infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate per 10,000 births</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Renal dysplasia</td>
<td>30.6</td>
<td>18.1</td>
</tr>
<tr>
<td>Renal agenesis</td>
<td>102</td>
<td>23.9</td>
</tr>
<tr>
<td>Ectopic kidney</td>
<td>30.6</td>
<td>18.1</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>346.9</td>
<td>16.9</td>
</tr>
<tr>
<td>Hydroureter</td>
<td>20.4</td>
<td>13.6</td>
</tr>
<tr>
<td>Ureteropelvic junction</td>
<td>30.6</td>
<td>16.2</td>
</tr>
<tr>
<td></td>
<td>obstruction</td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>20.4</td>
<td>51.1</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>275.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Obstructed meatus</td>
<td>20.4</td>
<td>68.1</td>
</tr>
<tr>
<td>Posterior urethral valves</td>
<td>10.2</td>
<td>14.6</td>
</tr>
</tbody>
</table>

* Adapted from Kumar and associates (2009).

In contrast to hypospadias, which is clinically detectable and is the most common renal/urinary anomaly among non-CH infants, most of the defects significantly more prevalent in patients with CH are not detectable on physical examination. Notably, about 4% of cases of CH also have hydronephrosis. Renal and urinary tract ultrasonography can readily detect these conditions, allowing early referral and treatment and reduce morbidities associated with end-stage renal disease. Consideration should be given for routine postnatal ultrasound examinations for all infants with CH. For infants going home to areas remote from a medical center, this can be especially important, as in the case in the vignette.

With the exception of pyloric stenosis, significantly increased rates of gastrointestinal anomalies are observed among patients with CH (Table 5).

Table 5: Gastrointestinal Anomalies in Congenital Hypothyroidism*

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Prevalence in CH</th>
<th>Comparison with non-CH infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate per 10,000 births</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Pancreatic atresia</td>
<td>30.6</td>
<td>18.1</td>
</tr>
<tr>
<td>Anal atresia</td>
<td>20.4</td>
<td>51.1</td>
</tr>
<tr>
<td>Anal stenosis</td>
<td>275.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Obstructed meatus</td>
<td>20.4</td>
<td>68.1</td>
</tr>
<tr>
<td>Obstructed meatus</td>
<td>10.2</td>
<td>14.6</td>
</tr>
</tbody>
</table>

* Adapted from Kumar and associates (2009).
Anomaly Prevalence in CH Comparison with non-CH Infants

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Prevalence in CH Rate per 10,000 births</th>
<th>Comparison with non-CH Infants Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal atresia/stenosis</td>
<td>51</td>
<td>32.0</td>
<td>13.3-77.4</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>10.2</td>
<td>7.3</td>
<td>1.0-59</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>40.8</td>
<td>31.5</td>
<td>11.8-84.5</td>
</tr>
<tr>
<td>Oral clefts</td>
<td>91.3</td>
<td>7.2</td>
<td>3.7-13.8</td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
<td>61.2</td>
<td>25.7</td>
<td>11.5-57.4</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>40.8</td>
<td>2.4</td>
<td>0.9-6.4</td>
</tr>
</tbody>
</table>

* Adapted from Kumar and associates (2009).

Most of these present or are clinically notable in the neonatal period. Although the prevalence rates would not mandate diagnostic testing for screening purposes, awareness of these increased risks can alert one to early symptoms that otherwise may be overlooked. Genital anomalies have not been described as being unusually prevalent in association with CH.

References:


American Board of Pediatrics Content Specification(s):

03_Cardiovascular: Know normal and abnormal morphogenesis and development of the heart and great arteries and the local regulatory factors involved

03_Cardiovascular: Know the neonatal developmental cardiac manifestations of maternal diseases and of common perinatal syndromes (e.g. congenital rubella)

07_Water_Salt_Renal: Recognize the clinical manifestations of anatomic abnormalities of the kidneys and urinary tract in infants

08_Endocrine_Metabolic_Thermal: Know the embryology and normal physiological function of the thyroid gland

08_Endocrine_Metabolic_Thermal: Know the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction

08_Endocrine_Metabolic_Thermal: Know the etiology and clinical manifestations of congenital hypothyroidism

11_Gastroenterology: Know the morphogenesis of the GI tract and factors that lead to congenital malformations
Question 4

You are called to the delivery room to evaluate a full-term neonate born after an uncomplicated pregnancy. The mother's obstetrician is concerned about a lesion (Figure 1) on the infant's neck.

Figure 1

A small amount of clear fluid is present at the base of the lesion. The lesion does not move when the infant swallows. The rest of the infant's physical examination findings are normal. The obstetrician asks you to explain the pathogenesis of the anomaly to the parents.

Of the following, the lesion in the Figure 1 is MOST likely the result of abnormal development of the:

- A. salivary duct
- B. second branchial arch
- C. third branchial arch
- D. thymus
- E. thyroid anlage

Incorrect: Correct Answer: B
Most congenital cervical anomalies are caused by abnormalities in the sequence of normal in utero development of cervical structures that result in cysts, sinuses, clefts, or fistulae. The differential diagnosis of congenital neck anomalies includes, in descending order of frequency, thyroglossal duct cysts, branchial cleft anomalies, dermoid cysts, ranulae, and median cervical clefts. The infant in the vignette has a median cervical cleft, a rare (50 cases described in English-language journals) midline neck lesion that can present at birth and may be associated with clefts of the lower lip, tongue, and mandible. Cervical clefts present as a cutaneous vertically oriented lesion with an overhanging cartilaginous tag (Figure 2, single arrow). Mucoid material can be expressed from the sinus orifice. Sinus tracts may end in blind pouches or extend downward to the sternum or upward to the mandible. A fibrous subcutaneous cord (Figure 2, double arrow) may extend upward toward the mandible and attach to one or two bony prominences on the inferior aspect of the mandible.

The cord, which becomes more prominent with time, may limit neck movement and makes early surgical intervention necessary. Recurrence risk is high despite complete surgical excision. Although the embryology of median cervical clefts is not entirely understood, it is believed that these clefts are caused by a failure of the paired second branchial arches to fuse in the midline sometime during the 3rd and 4th week of fetal development. Proposed mechanisms underlying improper fusion include:

- ischemia and necrosis from mechanical factors or vascular anomalies
- failure of mesenchyme to penetrate the midline, leading to a poor interaction between the mesoderm and ectoderm
- pressure on the cervical region by the pericardial roof

By the end of the 4th week of gestation, four well-defined and two rudimentary pairs of arches can be seen on the side of the future head and neck region. They are lined with ectoderm externally, endoderm internally, and mesoderm in between. Each arch contains a cartilaginous core, an aortic arch, and a definite cranial nerve. The ectoderm between the arches forms pharyngeal (branchial) clefts. Medially the arches are separated by pharyngeal pouches that approximate the corresponding cleft. In fish these structures form gills.
(‘branchium’ means ‘gill’), but in humans the clefts and pouches are gradually eliminated by mesenchyme to form the mature head and neck structures. The Table summarizes relationships between arches and their derivatives as well as the cranial nerve supply.

<table>
<thead>
<tr>
<th>Arch</th>
<th>Nerve</th>
<th>Muscle</th>
<th>Skeletal Structure</th>
<th>Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>V</td>
<td>Mastication muscles, mylohyoid, anterior digastric, tensor tympani, tensor velum palate</td>
<td>Malleus, incus, portion of mandible</td>
<td>Maxillary</td>
</tr>
<tr>
<td>2nd</td>
<td>VII</td>
<td>Facial expression muscles, stapedius, stylohyoid, posterior digastric</td>
<td>Staples, styloid, lesser cornu hyoid, upper body hyoid</td>
<td>Stapedial</td>
</tr>
<tr>
<td>3rd</td>
<td>IX</td>
<td>Stylopharyngeus</td>
<td>Greater cornu hyoid, lower body hyoid</td>
<td>Common and internal carotid</td>
</tr>
<tr>
<td>4th</td>
<td>X (superior laryngeal)</td>
<td>Constrictors of pharynx, cricothyroid</td>
<td>Laryngeal cartilage</td>
<td>Subclavian on right, arch of aorta on left</td>
</tr>
<tr>
<td>6th</td>
<td>X (recurrent laryngeal)</td>
<td>Intrinsic laryngeal muscles</td>
<td>Laryngeal cartilage</td>
<td>Pulmonary artery on right, ductus arteriosus on left</td>
</tr>
</tbody>
</table>

* Adapted from Pincus (2006).

Branchial anomalies are the result of incomplete obliteration of the arches, clefts, and pouches. Anomalies can present as cysts, sinuses, or fistulae. Third branchial arch anomalies are rare. Because the third and fourth pouches form the pharynx below the hyoid bone, sinuses and fistulae will enter the pyriform sinus. Third and fourth branchial anomalies may contain thymic tissue. Third arch anomalies can present as cystic structures located at the lower aspect of the neck along the anterior border of the sternocleidomastoid muscle. Third cleft lesions can present at any age and because of rapid enlargement they may cause tracheal compression and airway compromise. Because the neck lesion of the neonate in the vignette was in the midline, it is not a third branchial arch abnormality.

The third pharyngeal pouch gives rise to the primordial of the thymus gland during the 6th week of fetal life. By the 9th week the thymus has descended below the clavicles and the superior aspect of the thymus has regressed. Thymic remnants may persist as thymic cysts along the path of migration from the angle of the mandible. Most thymic cysts present as firm, nontender swellings in the lower third of the lateral neck just anterior to the sternocleidomastoid muscle. Approximately 50% will extend into the mediastinum. These thymic cysts are often mistaken for third branchial cleft cysts. In the vignette, the neonate’s lesion is in the midline and is not a cystic structure.

A ranula is a rare midline cervical cyst that is caused by the blockage of a sublingual salivary duct. Ranulae present in the floor of the mouth as cystic lesions that may affect sucking and swallowing. They may grow deep into the fascial planes of the neck (plunging ranula), but most are localized to the submental region.

Thyroglossal duct cysts develop from the remnants of the thyroid anlage. The thyroid develops from a diverticulum at the base of the tongue. As the embryo grows, the diverticulum moves caudally anterior to, posterior to, or through, the hyoid bone, to the midline of the neck where it fuses with components of the third and fourth branchial pouches. By 5 to 8 weeks of gestation, the thyroglossal duct obliterates, leaving a proximal remnant, the foramen cecum, and a distal remnant, the pyramidal lobe of the thyroid. If this duct fails to disappear before the hyoid bone is formed, a thyroglossal duct cyst will occur.
The most common presentation of a thyroglossal duct cyst is a painless cystic neck mass in the midline near the hyoid bone, and most (66%) are found immediately adjacent to the hyoid; however, they can be located anywhere along the path from the tongue to the thyroid. The mass usually moves with swallowing. More than 50% are identified before the age of 10 years, and 33% present with a concurrent infection or prior infection of the cysts. Thyroglossal cysts never have a natural fistula to the neck because the thyroglossal tract does not reach the neck surface. Approximately 25% will present with an externally draining sinus after an infected cyst ruptures or following surgical drainage.

References:


Foley DS, Fallat ME. Thyroglossal duct and other congenital midline cervical anomalies. *Semin Pediatr Surg.* 2006;15:70-75


**American Board of Pediatrics Content Specification(s):**

17_EENT_mouth_neck: Know the normal development of the nose, mouth, throat, and neck

17_EENT_mouth_neck: Know the clinical manifestations of branchial cleft cysts

17_EENT_mouth_neck: Know the clinical manifestations and approaches to therapy of neck masses in the newborn infant
April

ASSESSMENT PROGRESS:  Total Questions: 10  Questions Answered: 7  Correct Answers: 0

Question 7

A referring pediatrician calls you regarding a potential admission to the neonatal intensive care unit. She is concerned about a 3-day-old full-term infant who has developed increased respiratory distress; a culture of the placenta performed at the time of birth is positive for group B Streptococcus. The infant’s laboratory findings are shown.

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient Result (SI Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gas</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.10</td>
</tr>
<tr>
<td>Partial pressure of carbon dioxide, mm Hg (kPa)</td>
<td>10 (1.33)</td>
</tr>
<tr>
<td>Partial pressure of oxygen, mm Hg (kPa)</td>
<td>102 (13.5)</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L (mmol/L)</td>
<td>3.0 (3.0)</td>
</tr>
<tr>
<td>Base deficit, mEq/L (mmol/L)</td>
<td>26 (26)</td>
</tr>
<tr>
<td>Lactate, mg/dL (mmol/L)</td>
<td>1.3 (0.144)</td>
</tr>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>150 (150)</td>
</tr>
<tr>
<td>Potassium, mEq/L (mmol/L)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Chloride, mEq/L (mmol/L)</td>
<td>120 (120)</td>
</tr>
<tr>
<td>Carbon dioxide, mEq/L (mmol/L)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>White blood cell count, ×10^3/μL (×10^9/L)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>39.1 (0.39)</td>
</tr>
<tr>
<td>Platelet count, ×10^3/μL (×10^9/L)</td>
<td>52 (52)</td>
</tr>
<tr>
<td>Ammonia, μg/dL (μmol/L)</td>
<td>917 (538)</td>
</tr>
</tbody>
</table>

Of the following, the diagnosis MOST consistent with these data is:

- A. carbamyl phosphate synthetase deficiency
- B. methylmalonic acidemia
- C. ornithine transcarboxylase deficiency
- D. renal tubular acidosis
The infant in this vignette presents with an increased anion gap metabolic acidosis and elevated serum ammonia. Based on the available laboratory findings (increased anion gap acidosis with hyperammonemia), the most likely diagnosis is methylmalonic acidemia (MMA).

The anion gap is an important diagnostic tool in evaluating metabolic acidosis. The anion gap is estimated as $[\text{Na}^+] - (\text{[Cl}^{-}] + \text{[HCO}_3^{-}]$), with the normal value being approximately 8 to 16 mEq/L (8-16 mmol/L). The anion gap in this vignette is:

$$[150] - ([120] + [5]) = 25 \text{ mEq/L (25 mmol/L)}$$

Metabolic acidosis accompanied by an increased anion gap is caused by the accumulation of organic acids that titrate bicarbonate (Figure 1).

Figure 1: Approach to metabolic acidosis (from Enns and Packman [2001])

Organic acids that cause an increase in the anion gap include lactic acid, ketone bodies, and a number of unusual organic acids.

A number of inborn errors associated with increased anion gap acidosis are listed in the Table.

Table: Inborn Errors of Metabolism With Increased Anion Gap

<table>
<thead>
<tr>
<th>Organic Acidemias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propionic acidemia</td>
</tr>
<tr>
<td>Isovaleric acidemia</td>
</tr>
<tr>
<td>Condition</td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Methylmalonic acidemia</td>
</tr>
<tr>
<td>Holocarboxylase synthetase deficiency</td>
</tr>
<tr>
<td>Multiple acyl-CoA dehydrogenase deficiency</td>
</tr>
<tr>
<td>3-Hydroxyisobutyric acidemia</td>
</tr>
<tr>
<td>3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency</td>
</tr>
<tr>
<td><strong>Fatty Acid Oxidation Defects</strong></td>
</tr>
<tr>
<td>Short-chain acyl-CoA dehydrogenase (SCAD) defect</td>
</tr>
<tr>
<td>Medium-chain acyl-CoA dehydrogenase (MCAD) defect</td>
</tr>
<tr>
<td>Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) defect</td>
</tr>
<tr>
<td>Trifunctional protein deficiency</td>
</tr>
<tr>
<td>Very long-chain acyl-CoA dehydrogenase (VLCAD) defect</td>
</tr>
<tr>
<td>Carnitine uptake deficiency</td>
</tr>
<tr>
<td>Carnitine-acylcarnitine translocase (CAT) defect</td>
</tr>
<tr>
<td>Carnitine palmitoyltransferase 2 (CPT-2) defect</td>
</tr>
<tr>
<td><strong>Congenital Lactic Acidosis</strong></td>
</tr>
<tr>
<td>Pyruvate dehydrogenase deficiency</td>
</tr>
<tr>
<td>Pyruvate carboxylase deficiency</td>
</tr>
<tr>
<td>Mitochondrial respiratory chain disorders</td>
</tr>
<tr>
<td><strong>Tricarboxylic Acid Cycle Defects</strong></td>
</tr>
<tr>
<td>Fumaric aciduria</td>
</tr>
<tr>
<td>Alpha-ketoglutarate dehydrogenase deficiency</td>
</tr>
<tr>
<td><strong>Disorders of Gluconeogenesis</strong></td>
</tr>
<tr>
<td>Phosphoenolpyruvate carboxykinase deficiency</td>
</tr>
<tr>
<td>Fructose-1,6-bisphosphatase deficiency</td>
</tr>
</tbody>
</table>

The differential diagnosis for hyperammonemia is extensive; hyperammonemia is a characteristic finding in urea cycle defects, organic acidemias, fatty acid oxidation defects, and liver dysfunction. Evaluation for metabolic acidosis and anion gap can help elucidate the cause of hyperammonemia in this infant.

An algorithm for the approach to hyperammonemia is presented in **Figure 2**.

**Figure 2: Approach to the investigation of hyperammonemia. CPS = carbamyl phosphate synthetase; HHH = hyperammonemia-hyperornithinemia-homocitrullinuria syndrome; LPI = lysinuric protein intolerance; NAGS = N-acetylglutamate synthetase; OTC = ornithine transcarbamylase; THAN = transient hyperammonemia. (From Enns and Packman [2001]).**

(CLICK HERE to view larger version)
When hyperammonemia presents with acidosis, the underlying cause is commonly found among the conditions listed as the organic acidemias. Of the choices presented in the vignette, only MMA is classified as an organic acidemia.

Organic acidemias, also known as organic acidurias, are a group of disorders characterized by increased excretion of organic acids in urine. Newborns with organic acidemia typically present after an initial period of wellness with poor feeding, vomiting, hypotonia, and increasing lethargy. If undetected or left untreated, this quickly progresses to coma. Often this presentation is mistaken for sepsis.

Infants typically have severe metabolic acidosis with an increased anion gap, ketosis, hypoglycemia, and hyperammonemia. Other common findings include hypoglycemia and electrolyte and other abnormalities associated with volume depletion. A complete blood count with differential often demonstrates neutropenia, thrombocytopenia, or pancytopenia, which occur secondary to bone marrow suppression.

Methylmalonic acidemia (MMA) is caused by a deficiency of the adenosylcobalamin-dependent enzyme methylmalonyl CoA mutase or its cofactor, cobalamin, which is required for the isomerization of methylmalonyl CoA to succinyl CoA. The impaired metabolism of isoleucine, methionine, threonine, valine, and odd-chain fatty acids generates methylmalonic acid. The incidence of MMA is 1 in 48,000 live births and inheritance is autosomal recessive. The genetic locus has been assigned to chromosome 6p12. At least eight different defects, ranging from undetectable mutase activity to defects in cobalamin transport, reduction, and synthesis, can cause MMA.

Associated clinical features that may be present at birth include microcephaly, hydrocephalus, pigmentary retinopathy, nystagmus, or megaloblastic anemia. Facial dysmorphism is occasionally associated with MMA and includes high forehead, broad nasal bridge, epicantal folds, long, smooth philtrum, and triangular mouth. Infants eventually develop dehydration, failure to thrive, developmental delay, skin lesions, and hepatomegaly. The diagnosis of MMA is made by measurement of organic acids (methylmalonic acid) in the urine using gas chromatography–mass spectroscopy (GC-MS).

Treatment consists of a diet restricted in protein, odd-chain fatty acids, and polyunsaturated fat. Serial measurements of plasma MMA concentrations may be helpful to guide management. Hydroxycobalamin is given until the type of MMA is known. Infants with defects in the synthesis of adenosylcobalamin often respond to this treatment, whereas those with mutase defects do not. Treatment with hemodialysis to reduce serum ammonia is imperative in the immediate term.
Patients with MMA can die in the newborn period or during a later episode of metabolic decompensation. Although those who survive often have significant neurodevelopmental handicap, normal cognitive development can occur. Computed tomography and magnetic resonance imaging of the brain demonstrate widening of sulci and fissures, delayed myelination, and involvement of basal ganglia and white matter. Renal disease, which may result in chronic renal failure, can be caused by tubulointerstitial injury due to methylmalonyl-CoA or its precursors or uric acid nephropathy. Other complications include pancreatitis, recurrent infections that may be related to neutropenia, and hypoglycemia.

Organic acidemias can be distinguished from urea cycle defects. Organic acidemias are associated with more significant metabolic acidosis, especially early in the course of illness. Respiratory alkalosis usually accompanies hyperammonemia in urea cycle disorders, except in cases of shock or secondary infection. The respiratory alkalosis is caused by hyperpnea induced by the elevated ammonia concentration. Of the options in the vignette, carbamyl phosphate synthetase deficiency and ornithine transcarboxylase deficiency are classified as urea cycle defects, both of which result in hyperammonemia more likely with alkalosis than with metabolic acidosis.

Renal tubular acidosis results from a loss of bicarbonate and presents with a normal anion gap acidosis.

Sepsis is always an important consideration in a decompensating newborn; the acidosis is usually secondary to elevated lactate; the infant in this vignette has a normal lactate concentration. As infection can increase metabolic demand, sepsis may coincide with or precipitate the onset of metabolic crisis in many of the inborn errors of metabolism and therefore should be considered.

References:


American Board of Pediatrics Content Specification(s):

07_Water_Salt_Renal: Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants

08_Endocrine_Metabolic_Thermal: Know the causes and differential diagnosis of metabolic encephalopathy

08_Endocrine_Metabolic_Thermal: Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle

08_Endocrine_Metabolic_Thermal: Know the clinical manifestations, laboratory features, and treatment of organic acid disorders
May

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Question 8

A 10-day-old male infant, who weighed 980 g at birth at an estimated gestational age of 28 weeks, is in an incubator. The infant is in no distress and breathing spontaneously in room air. He is receiving full enteral feeding of human milk by continuous orogastric infusion. He is receiving no medications. The ambient temperature in the incubator is 32ºC (89.6ºF) and the humidity is 72%. The infant's abdominal skin temperature is 36.5ºC (97.7ºF) and axillary temperature is 36.8ºC (98.2ºF).

An inadvertent malfunction of the electrical outlet makes the incubator temperature drop to 26ºC (78.8ºF) over 20 minutes. As you correct the problem, you measure the infant’s core body temperature by a rectal temperature probe, which reads 37ºC (98.6ºF). The infant’s abdominal skin temperature now reads 36ºC (96.8ºF). The infant remains sound asleep in no distress; no shivering or voluntary muscle activity is visible.

You suspect cold-induced thermogenesis by brown fat, coupled with peripheral vasomotor thermal adaptation, as the mechanism responsible for the infant’s maintenance of normal core body temperature despite cold exposure.

Of the following, the MOST accurate statement regarding the role of brown fat in thermogenesis is that brown fat:

- A. cells contain few mitochondria and single large fat vesicles
- B. depots are located largely in the abdominal wall and the flanks
- C. localization is best achieved with magnetic resonance imaging
- D. mass is correlated positively with body mass index and body fat percentage
- E. metabolism is mediated mainly through uncoupling protein 1

The infant in this vignette can maintain the core body temperature within normal limits despite a brief exposure to cold. This ability is characteristic of homeothermic behavior, which allows body temperature to be maintained within a narrow stable range despite fluctuations in environmental temperature. Two classes of the animal kingdom, the birds and the mammals, are homeothermic; other species are poikilothermic, meaning the body temperature in these species fluctuates with the environmental temperature.
To understand homeothermic behavior, it is important to review heat balance (Figure 1).

**Figure 1: Heat balance**

Heat balance has two arms: heat production and heat loss. Heat balance is positive when heat production exceeds heat loss, and the net result is a progressive increase in body temperature (hyperthermia). Conversely, heat balance is negative when heat loss exceeds heat production, and the net result is a progressive decrease in body temperature (hypothermia). When heat production and heat loss are matched, the heat balance reflects a zero balance, and the net result is a constant central body temperature. The infant in this vignette has maintained a zero heat balance in adaptation to the cold exposure through a combination of increased heat production and decreased heat loss.

The elements of heat balance in their approximate relative proportions in the newborn are shown in Figure 1.

The elements of heat production include the following:

- Basal heat production: Generation of heat with normal metabolic activity under thermoneutral conditions (no cold or heat exposure)
- Supplemental heat production with voluntary muscle activity: Generation of additional heat under cold exposure with voluntary movements
- Supplemental heat production with shivering: Generation of additional heat under cold exposure with involuntary tonic or rhythmic muscle activity, visible or detected on electromyography
- Supplemental heat production with brown fat: Generation of additional heat under cold exposure by nonshivering thermogenesis

The infant in this vignette is likely to have resorted to brown fat–mediated nonshivering thermogenesis in an effort to maintain heat balance during cold exposure.

The elements of heat loss include the following:

- Conduction: Transfer of heat from body surface by contact with another surface, such as mattress or clothing
- Convection: Transfer of heat from body surface to surrounding environment influenced by air currents or body oscillations
• Radiation: Transfer of heat from body surface to another surface, such as incubator wall, when the two surfaces are not in contact with each other

• Evaporation: Dissipation of heat with insensible water loss by evaporation from the skin and respiratory tract

The infant in this vignette, in an effort to maintain heat balance during cold exposure, is likely to have reduced heat loss by an adaptive mechanism of peripheral vasoconstriction through sympathetic mediation. A fall in the abdominal skin temperature (peripheral temperature), in the face of a constant core body temperature (central temperature), is suggestive of this adaptive response.

Brown fat–induced nonshivering thermogenesis begins with sensing of the cold stress through peripheral cutaneous thermosensors (abundant throughout the skin) and central deep body thermosensors (located largely in the preoptic region of the brain and the anterior hypothalamus). The subsequent events in the brown fat cell (Figure 2) include the following:

• Stimulation of adrenergic neurons and release of catecholamines (mainly norepinephrine)
• Stimulation of β3-adrenergic receptors on the cell surface
• Release of cyclic adenosine monophosphate (cAMP) into the nucleus
• Binding of cAMP to cAMP response element (CRE) and transcription of type 2 5′-deiodinase (D2) – a thyroid hormone enzyme
• Conversion of intracellular thyroid hormone thyroxine (tetraiodothyronine, T4) to active thyroid hormone (triiodothyronine, T3) by D2
• Binding of T3 to thyroid hormone response element (TRE) and transcription of uncoupling protein 1 (UCP1)
• Translocation of UCP1 into the mitochondria
• Leakage of protons from the inner mitochondrial membrane by UCP1
• Release of heat from metabolism of free fatty acids and, to a lesser extent, glucose within the mitochondria

Figure 2: Brown fat metabolism. cAMP = cyclic adenosine monophosphate; CRE = cAMP response element; T3 = triiodothyronine; T4 = tetraiodothyronine; and UCP1 = uncoupling protein 1

Uncoupling protein 1 (formerly called thermogenin) is a key mediator of brown fat metabolism. UCP1 is a 32-kD protein, a member of the family of mitochondrial carrier proteins. The gene for UCP1 is located on chromosome 4 in humans. When thermogenesis is needed, UCP1 is activated as shown in the aforementioned sequence. When thermogenesis is
not needed, UCP1 is inactivated by its binding to adenosine triphosphate present in the cytosol of the brown fat cell.

Brown fat cells have granular cytoplasm containing abundant mitochondria and multiple small fat vesicles (Figure 3).

Figure 3: Brown fat versus white fat

In contrast, white fat cells have clear cytoplasm, paucity of mitochondria, and a single large fat vesicle in each cell. Brown fat cells show immunofluorescence when stained with UCP1-specific antibodies, whereas no such staining is seen in white fat cells. Also, brown fat cells show colocalization of UCP1 when stained with a mitochondrial marker, cytochrome oxidase subunit 1, whereas minimal mitochondrial staining is seen in white fat cells. These immunohistochemical techniques are used to differentiate brown fat cells from white fat cells.

Brown fat is found in many depots in the body. The major depots are located in the interscapular, supraclavicular, and cervical regions. Additional depots are located in the superior mediastinal, pericardiac, paraspinal, and perirenal regions. In contrast to white fat, brown fat typically is not located in the abdominal wall or the flanks. In general, brown fat depots are more abundant in the newborn than in the adult, which reflects a higher dependance of the neonate on brown fat for thermogenesis.

Brown fat is best localized using positron-emission tomography (PET) after the administration of a PET-tracer $^{18}$F-fluorodeoxyglucose. This localization is enhanced by integration of the PET scan with computed tomography.

Recent studies in human adults have shown that brown fat mass correlates negatively with body mass index and body fat percentage. In other words, the leaner the individual, the higher is the brown fat activity. This observation refutes the previous notion that brown fat has no role in the metabolic regulation in the adult. On the contrary, it suggests that brown fat may be metabolically important in adults, much as in neonates, and that brown fat may be a target for modulation in the treatment of obesity.

References:


van Marken Lichtenbelt, Vanhommerig JW, Smulders NM, et al. Cold-activated brown adipose


Related readings from Neoreviews.org


**American Board of Pediatrics Content Specification(s):**

06_Nutrition: Know the physiology of fat digestion (and) absorption (and metabolism) in newborn infants

08_Endocrine_Metabolic_Thermal: Know the mechanisms of heat gain and loss

08_Endocrine_Metabolic_Thermal: Know the causes, metabolic consequences, and treatment of infants with hypothermia

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A 2-kg female infant is born at 34 weeks’ gestation after induction of labor secondary to worsening maternal preeclampsia. The pregnancy had been complicated by hyperemesis gravidarum and a diagnosis of maternal Graves disease. Maternal treatment with propylthiouracil was discontinued 1 week before delivery when laboratory studies demonstrated a euthyroid state.

Of the following, this infant’s risk for neonatal thyroid dysfunction is MOST related to:

- A. duration of maternal treatment with propylthiouracil
- B. female sex
- C. maternal thyroid function at delivery
- D. maternal thyroid-stimulating hormone-receptor antibody titer
- E. umbilical cord free thyroxine concentration

**Incorrect:**

Correct Answer: D
and TSAb. Although maternal Graves disease occurs in 0.1% to 0.4% of pregnancies, variability in the uptake and metabolism of thyroid antibody results in only 1% to 1.5% of offspring affected. As a result, neonatal hyperthyroidism is a rare disorder, occurring in as few as 1 in 4,000 to 1 in 50,000 deliveries.

Fetal outcome is related to the control of maternal thyrotoxicosis, and complications are increased when mothers remain hyperthyroid in the second half of pregnancy. Intrauterine growth restriction (IUGR), accelerated bone maturation, and fetal tachycardia are common findings. Ultrasonography after 27 weeks' gestation may demonstrate a fetal goiter. Intrauterine death occurs in 5% to 7% of pregnancies in women receiving treatment for thyrotoxicosis, and in 24% of untreated pregnancies. Fetal hydrops secondary to cardiac failure accounts for the high mortality. Preeclampsia develops in approximately 14% of pregnant women with uncontrolled hyperthyroidism. Preterm delivery occurs in 11% of treated and 53% of untreated pregnancies.

In the neonate, signs and symptoms of thyrotoxicosis may manifest at birth or may be delayed for several days to as late as 45 days after birth. Maternal TSAbs continue to stimulate the neonate's thyroid after delivery, but maternal antithyroid medications, which cross the placenta and inhibit the fetal thyroid, can delay symptoms for several days. Furthermore, the presence of TSAb may temporarily antagonize and blunt the effect of stimulating antibody. Symptoms of thyrotoxicosis are usually apparent by 10 days of age.

The clinical manifestations of hyperthyroidism in the neonate include metabolic consequences as well as abnormalities in the growth and maturation of thyroid hormone-dependent tissues such as the brain and skeleton. A goiter may be present, and when large, may cause airway obstruction. Additional signs and symptoms include:

- intranuclear growth restriction
- irritability and jitteriness
- voracious appetite, diarrhea, weight loss, sweating, and flushing
- periorbital edema, lid retraction, and exophthalmos
- tachycardia, arrhythmias, cardiac failure, and systemic and pulmonary hypertension
- persistent acrocyanosis
- hepatosplenomegaly, lymphadenopathy, thymic enlargement
- jaundice and hepatic cholestasis
- thrombocytopenia
- hyperviscosity
- advanced bone age, microcephaly, and craniosynostosis

The greatest risk for fetal or neonatal thyrotoxicosis occurs when the maternal titer of thyroid-stimulating antibody is five times the upper limit of normal, though disease may occur at much lower antibody titers. Maternal antithyroid drug treatment and maternal thyroid function at delivery, affected by antithyroid treatment, are not surrogates for thyroid-stimulating antibody titers and poorly predict disease in the neonate. Furthermore, asymptomatic women with a history of ablative or surgical treatment for Graves disease can still produce high titers of antibody many years later, placing their offspring at risk. However, maternal thyrotoxicosis developing or requiring treatment during gestation, antithyroid treatment in the third trimester, and a family history of TSH receptor mutation should heighten suspicion for fetal and neonatal disease. Thyrotoxicosis in the neonate displays no predilection for either sex.

The infant at risk for thyrotoxicosis should be assessed with umbilical cord blood thyroid function studies (free $T_3$, free $T_4$, and TSH). Thyroid-stimulating immunoglobulins may be measured and help to predict subsequent hyperthyroidism. At birth, the infant of a mother with Graves disease also may be hypothyroid or euthyroid, depending on transplacental passage of antithyroid medications, TSAb, and TSAb. Close observation and frequent physical examination are indicated. Reassessment should be considered at 48 hours and at 1 to 2 weeks of age.

Treatment of the hyperthyroid neonate aims at normalizing thyroid function and minimizing clinical symptoms. When untreated, mortality is 12% to 20%.

- Infants with laboratory abnormalities without overt clinical symptoms may be closely observed.
- Antithyroid thionamides (propylthiouracil [PTU] and carbimazole) block the
organification of iodine and the coupling of iodothyronine residues, thereby blocking thyroid hormone synthesis. PTU also inhibits the peripheral deiodination of T<sub>4</sub> to the more active form T<sub>3</sub>. Because these drugs block the synthesis and not the release of thyroid hormones, a clinical response may not occur until depletion of stored thyroid hormone.

- Iodine solution, which inhibits thyroid hormone release, in addition to suppressing synthesis, may be used in conjunction with antithyroid thionamides. Because this approach results in complete thyroid suppression, thyroid hormone replacement with levothyroxine is indicated to achieve a euthyroid state. Iopanoic acid and ipodate sodium, used as contrast material in gallbladder imaging studies, also inhibit extrathyroidal conversion of T<sub>4</sub> to T<sub>3</sub>, and their iodine content inhibits thyroid hormone secretion.
- β-blockers such as propranolol help suppress hyperthyroid symptoms caused by adrenergic stimulation. β-blockers also inhibit the peripheral conversion of T<sub>4</sub> to T<sub>3</sub>. Close monitoring for adverse effects such as hypoglycemia, bradycardia, and hypotension is necessary.
- Digoxin and diuretics may be indicated for cardiac failure.
- Prednisone has been used to treat severely thyrotoxic newborns by suppressing deiodination of T<sub>4</sub> to T<sub>3</sub> and compensating for thyroid-induced hypercatabolism of endogenous glucocorticoids.
- Sedatives may be helpful in managing irritability and restlessness.

Neonatal thyrotoxicosis secondary to maternal Graves disease usually undergoes remission after 8 to 10 weeks and treatment, if needed, usually can be stopped at that time. Thyroid antibody concentrations decrease over time, dissipating by 8 to 20 weeks of age, but may be detectable until 6 months of age. Persistent hyperthyroidism suggests activating mutations in the TSH receptor and may require ablative treatment. Long-term effects of neonatal thyrotoxicosis include craniosynostosis, and impaired cognitive and psychomotor functions. Overall growth failure has been more consistently observed among patients with activating mutations in the TSH receptor.

References:
Ogilvy-Stuart AL. Neonatal thyroid disorders. Arch Dis Child Fetal Neonatal Ed. 2002;87:F165-171
Zimmerman D. Fetal and neonatal hyperthyroidism. Thyroid. 1999;9:727-733
Related readings from Neoreviews.org
American Board of Pediatrics Content Specification(s):
01_Maternal_Fetal: Know the effects on the fetus and/or newborn infant of maternal immunologic diseases and their management
08_Endocrine_Metabolic_Thermal: Know the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction
08_Endocrine_Metabolic_Thermal: Identify the etiology, clinical manifestations, laboratory
November

A 2-day-old male infant, who weighed 4,250 g at birth at an estimated gestational age of 38 weeks, is being evaluated for pallor and an abdominal mass in each flank. Maternal history included gestational diabetes. The vaginal delivery of the infant was prolonged because of a difficult breech extraction. The infant’s Apgar scores were 8 and 9 at 1 and 5 minutes after birth, respectively.

Physical examination of the infant reveals a well-appearing child with no respiratory or cardiac symptoms, skin rash, or enlarged liver and spleen. A soft, nontender, abdominal mass is palpable in each flank with discoloration of the overlying skin.

A complete blood count reveals: hematocrit, 30% (0.3); hemoglobin, 10.0 g/dL (6.2 mmol/L); erythrocyte count, 3.9×10⁶ /μL (3.9×10¹²/L); leukocyte count, 8.0×10³/μL (8.0×10⁹/L) with normal differential; and platelet count, 268×10³/μL (268×10⁹/L). Serum chemistry tests show normal electrolytes, urea nitrogen, creatinine, and liver function. Abdominal ultrasonography (Figures 1 and 2) reveals blood-engorged right and left adrenal glands.

Figure 1: Abdominal ultrasonography shows a sonolucent mass in the right adrenal gland (outlined by arrows) indicative of right adrenal hemorrhage.
Figure 2: Abdominal ultrasonography shows a sonolucent mass in the left adrenal gland (outlined by arrows) indicative of left adrenal hemorrhage.
Of the following, the MOST accurate statement regarding neonatal adrenal hemorrhage is that the hemorrhage:

- **A.** involves both adrenal glands more frequently than either the right or left adrenal gland
- **B.** manifests typically with hypovolemic shock and adrenal insufficiency
- **C.** occurs most commonly as a result of birth trauma
- **D.** requires intravenous angiography for establishment of the diagnosis
- **E.** warrants exploratory laparotomy for surgical intervention

**Correct**

Neonatal adrenal hemorrhage is more common than previously suspected. Based on autopsy studies, Snelling and Erb reported an incidence of 0.5 per 1,000 cases in 1935, whereas DeSa and Nicholls reported an incidence of 1.4 per 1,000 cases in 1972. Based on abdominal ultrasonographic screening of live newborns, Felc reported an incidence of 1.9 per 1,000 births in 1995.

The most common cause of neonatal adrenal hemorrhage is birth trauma, accounting for an estimated 30% of cases. The history of difficult breech extraction in the macrosomic infant of a diabetic mother in this vignette is suggestive of this cause. The fetal adrenal gland is vulnerable to traumatic hemorrhage because of its large size and increased vascularity. Other causes of
neonatal adrenal hemorrhage include hypoxia-ischemia-reperfusion injury, sepsis (including neonatal tuberculosis and congenital syphilis), and bleeding diathesis (including disseminated intravascular coagulopathy and hemorrhagic disease of the newborn). No precipitating event may be identifiable in some cases of neonatal adrenal hemorrhage.

Contrary to the observation in the infant in this vignette, bilateral adrenal hemorrhages are infrequent in the neonate, accounting for only 10% to 15% of all cases. Among the much larger percentage of cases of unilateral adrenal hemorrhage, the right adrenal gland is involved in 70% of cases. This predilection of the right adrenal gland to hemorrhage may be attributed to two factors: location and venous drainage. The location and narrow confinement of the right adrenal gland between the liver and spine may make the gland vulnerable to the effects of increased abdominal pressure, as seen during a difficult delivery. The right adrenal vein empties directly into the inferior vena cava, whereas the left adrenal vein empties indirectly into the inferior vena cava via the left renal vein. The direct emptying into the inferior vena cava may make the right adrenal gland vulnerable to the changes in central venous pressure that can be transmitted to the gland.

The clinical manifestations of neonatal adrenal hemorrhage vary with the extent of the hemorrhage. In mild cases, the clinical presentation may be occult and characterized by an incidental finding of adrenal hemorrhage on abdominal ultrasonography or that of adrenal calcification on abdominal radiography. In moderate cases, as in the infant in this vignette, the typical clinical findings include an abdominal flank mass with overlying skin discoloration, anemia from blood loss, and jaundice from breakdown of red blood cells in the hematoma. In severe cases, extensive adrenal hemorrhage may lead to symptoms and signs of hypovolemic shock and of adrenal insufficiency. Rarely, rupture of the capsule of the adrenal gland may lead to intraperitoneal leakage of blood, which in male infants may manifest as a scrotal hematoma. Most cases of neonatal adrenal hemorrhage are of mild-to-moderate severity; hence, the typical manifestations are an abdominal mass, anemia, and jaundice.

Abdominal ultrasonography is important for the diagnosis of neonatal adrenal hemorrhage. In the initial stages of the hemorrhage, the typical ultrasonographic findings include a sonolucent or solid mass above the kidney, which represents diffuse clotted blood in the adrenal gland. In the subsequent stages of the hemorrhage, typically within 1 week, the adrenal mass changes from a solid to a cystic appearance, coincident with gradual lysis of the clot. Adrenal calcification is often seen several weeks after an adrenal hemorrhage. Abdominal computed tomography and magnetic resonance imaging are adjunct diagnostic modalities that may be required to differentiate an adrenal hemorrhage from an adrenal tumor such as a neuroblastoma or a neural crest tumor. Intravenous angiography is not indicated for the diagnosis or follow-up of neonatal adrenal hemorrhage.

In most cases, neonatal adrenal hemorrhage resolves spontaneously and warrants no treatment beyond general supportive measures such as fluid-electrolyte management, blood replacement, phototherapy, and serial observation. The decision for surgical intervention is dictated by the extent and location of the hemorrhage. In rare cases in which the blood loss exceeds blood replacement or the intraperitoneal extension of the adrenal hemorrhage compromises the function of other abdominal organs, an exploratory laparotomy for surgical intervention may be indicated. Surgical interventions may include evacuation of the hematoma, adrenal vessel ligation, or in extreme cases, adrenalectomy with or without nephrectomy.

References:


**American Board of Pediatrics Content Specification(s):**

01_Maternal_Fetal: Know the neonatal complications of abnormal presentations (breech, shoulder dystocia, etc)

11_Gastroenterology: Know the etiology, clinical and laboratory features, and management of abdominal masses in the neonate

Continue

Page 6 of 10
December

A 3-day-old term male infant is admitted for vomiting, lethargy, seizures, and tachypnea. He is found to have hyperammonemia.

Of the following, the laboratory study MOST helpful in differentiating urea cycle defects from other causes of hyperammonemia is:

- A. carnitine (plasma)
- B. citrulline (plasma)
- C. lactate (plasma)
- D. organic acids (urine)
- E. phenylacetylglutamine (urine)

Correct Answer: D

The metabolic diseases that present during the neonatal period, in general, can be categorized into two groups:

- Disorders affecting the intermediary metabolism of small molecules such as glucose, pyruvate, lactate, amino acids, organic acids, ammonia, and mitochondrial respiration and oxidative phosphorylation
- Disorders involving complex molecules such as storage diseases

Disorders affecting small molecules often present as acute, life-threatening illnesses or acute encephalopathy (eg, seizures, stupor/coma, vomiting, hypothermia, tone abnormalities, apnea, and tachypnea). Symptoms are caused by accumulation of toxic metabolites (such as ammonia, organic acids), hypoglycemia, or failure of oxidative phosphorylation with diminished production of energy molecules and accumulation of lactic acid. The severity of symptoms is a function of the degree of the enzyme deficiency.

Disorders involving complex molecules include diseases with storage of intermediary metabolites (glycogen storage diseases, such as Niemann-Pick Disease), peroxisomal disorders (such as Zellweger syndrome), connective tissue defects (such as osteogenesis imperfecta), cholesterol metabolism defects (such as Smith-Lemli-Opitz syndrome), and congenital glycosylation defects (such as congenital disorder of glycosylation Ia). Such
disorders may present in utero through infancy. Disorders of complex molecules frequently present with unique or characteristic physical findings such as dysmorphic features, hepatomegaly, and ichthyosis. Of the disorders of complex molecules, only the glycogen storage diseases are associated with nonimmune hydrops.

Hyperammonemia presenting during the neonatal period is associated with defects in metabolic pathways involving small molecules. Elevated concentrations of ammonia may be caused by urea cycle defects; organic acid disorders; perinatal asphyxia; hepatic failure; total parenteral nutrition, and in the rare disorders of lysine protein intolerance; hyperornithinemia, hyperammonemia, and homocitrullinemia; and transient hyperammonemia of prematurity. Hyperammonemia associated with hepatic dysfunction or parenteral nutrition is usually mild and without clinical effect, and the odds of a patient having a rare disorder are low. Thus, the usual clinical challenge is differentiating the urea cycle defects from organic acid disorders. Clinical onset within days of birth and symptoms of seizures, tone abnormalities, and stupor/coma may be similar in both of these defect categories. Laboratory clues to the diagnosis include measurement of organic acids in urine and metabolic acidosis (organic acid disorders) and alkalosis/absent metabolic acidosis (urea cycle defects). The presence of a specific organic acid profile may be diagnostic (Figure 1).

Figure 1: Algorithm for investigation of hyperammonemia in neonates. (Adapted from Volpe [2008] and Enns and Steiner [2005].) (CLICK HERE to view at full size)

If organic acids are absent in the urine in the presence of hyperammonemia, a defect in the urea cycle is most likely. If urinary organic acids and hyperammonemia are present, a defect in metabolism of fatty acids, organic acids, or lactate is likely to be present.

Plasma citrulline is a key laboratory measurement in differentiating the defects in the urea cycle (Figure 1). The concentration of citrulline and presence of arginosuccinic acid (urine and plasma) and orotic acid (urine) further differentiate specific urea cycle defects.

Measurement of lactate and pyruvate, specific organic acids (urine), and dicarboxylic acids (urine) allow categorization of the underlying causes for the constellation of hyperammonemia, organic aciduria, and metabolic acidosis (Figure 1). The lactate-pyruvate ratio is helpful in differentiating pyruvate metabolic defects from mitochondrial defects. The presence of specific organic acids in urine and plasma are diagnostic of organic acid disorders; urinary dicarboxylic acids can define specific fatty acid oxidation defects.

Carnitine is important for proper function of the fatty acid oxidation cycle and in scavenging toxic metabolites in disorders of fatty acid oxidation and organic acid metabolism. Carnitine is responsible for transporting long-chain fatty acids across the inner mitochondrial membrane. It is present in most diets and synthesized in liver and kidney. Primary and secondary deficiencies exist. Elevations of carnitine esters may be a clue to the presence of fatty acid oxidative disorders and organic acidemias. By means of esterification, carnitine also detoxifies some intermediary metabolites that accumulate in a number of metabolic disorders. Carnitine is not directly involved with the urea cycle or the alternative pathways for ammonia excretion.
Phenylacetylglutamine and hippurate are secondary excretory molecules for nitrogen in the presence of urea cycle defects and organic acid disorders such as propionic acidemia and methylmalonic acidemia (Figure 2).

Figure 2: Nitrogen excretion pathways. (Adapted from Volpe [2008].) (CLICK HERE to view at full size)

In these latter disorders, coenzyme A esters accumulate and inhibit the activity of carbamyl phosphate synthetase, the enzyme responsible for synthesis of carbamyl phosphate from ammonia and N-acetylglutamate. Carbamyl phosphate is converted by ornithine transcarbamylase to citrulline and eventually to urea.

References:


American Board of Pediatrics Content Specification(s):
08_Endocrine_Metabolic_Thermal: Know the causes and differential diagnosis of metabolic encephalopathy
08_Endocrine_Metabolic_Thermal: Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids
08_Endocrine_Metabolic_Thermal: Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids
08_Endocrine_Metabolic_Thermal: Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle
08_Endocrine_Metabolic_Thermal: Know the clinical manifestations, laboratory features, and treatment of organic acid disorders
15_Neurology: Know the causes and management of metabolic encephalopathies in newborn infants
A 6-week-old female infant, who weighed 2,140 g at birth at an estimated gestational age of 34 weeks, is being evaluated for fluid-electrolyte imbalance. She has had primary closure of gastroschisis at 1 week of age. Enteral feeds have been delayed because of feeding intolerance, which has led to exclusive parenteral nutrition through a central venous catheter. Her mean fluid intake is approximately 150 mL/kg per day. For the last 2 days, the infant has been receiving amphotericin B treatment for a positive blood culture for *Candida albicans*. She is observed to have numerous wet diapers.

Physical examination of the infant reveals a slightly sunken fontanel and loss of skin turgor. She has no apparent malformations or dysmorphic features. Neurologic examination reveals normal tone, activity, and reflexes. The infant is breathing spontaneously in room air without distress and has no signs of cardiac dysfunction. Abdominal examination finds no hepatosplenomegaly or masses. Cranial and renal ultrasonographic studies are normal.

Serum chemistry reveals the following:

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient Result (SI Unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>156 (156)</td>
</tr>
<tr>
<td>Potassium, mEq/L (mmol/L)</td>
<td>4.8 (4.8)</td>
</tr>
<tr>
<td>Chloride, mEq/L (mmol/L)</td>
<td>102 (102)</td>
</tr>
<tr>
<td>Glucose, mg/dL (mmol/L)</td>
<td>84 (4.7)</td>
</tr>
<tr>
<td>Calcium, mg/dL (mmol/L)</td>
<td>9.2 (2.3)</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL (mmol/L)</td>
<td>18 (6.4)</td>
</tr>
<tr>
<td>Creatinine, mg/dL (μmol/L)</td>
<td>0.5 (44)</td>
</tr>
<tr>
<td>Osmolality, mOsm/kg (mmol/kg)</td>
<td>312 (312)</td>
</tr>
</tbody>
</table>

The infant’s mean urine output is 9.6 mL/kg per hour in the last 24 hours. Other urine measurements are as follows: specific gravity, 1.002; osmolality, 254 mOsm/kg (254 mmol/kg); and sodium, 28 mEq/L (28 mmol/L). The urine is negative for protein, glucose, or bacteria.

Of the following, the diabetes insipidus suspected in this infant is MOST likely to be:

- **A.** dipsogenic polyuric
- **B.** primary nephrogenic
- **C.** primary neurogenic
- **D.** secondary nephrogenic
- **E.** secondary neurogenic

Incorrect
Correct Answer: D
Diabetes insipidus (DI), excessive production of dilute urine, is characterized by the excretion of urine in excess of 150 mL/kg per 24 hours in infants. Typically, the urine specific gravity is 1.005 or less, and the urine osmolality is less than 300 mOsm/kg (300 mmol/kg). The serum sodium concentration is greater than 145 mEq/L (145 mmol/L), and the serum osmolality is greater than 290 mOsm/kg (290 mmol/kg). The infant in this vignette with hypernatremic dehydration has all of these features of DI.

Diabetes insipidus is caused by a deficiency of arginine-vasopressin (AVP) secretion or action. DI is designated as:

- neurogenic (also called hypothalamic or central) DI, when there is partial or total deficiency of AVP secretion from the neurohypophysis
- nephrogenic (also called renal) DI, when there is partial or total renal resistance to the antidiuretic action of AVP
- dipsogenic polyuric DI, when there is an excessive fluid intake with resultant suppression of AVP secretion

Neurogenic DI is classified as primary (genetic defect of AVP secretion) or secondary (acquired defect of AVP secretion). Central nervous system defects causing DI involve one or more of the following factors of AVP regulation and synthesis: hypothalamic osmoreceptors, supraoptic and paraventricular nuclei, and supraoptic-hypophyseal tract. Most infants with neurogenic DI have lesions of the pituitary gland or of the supraoptic and paraventricular nuclei. The causes of neurogenic DI are summarized in Tables 1 and 2.

### Table 1: Primary Neurogenic Diabetes Insipidus*

<table>
<thead>
<tr>
<th>Congenital malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septo-optic dysplasia</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
</tr>
<tr>
<td>Midline craniofacial defects</td>
</tr>
<tr>
<td>Familial pituitary hypoplasia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genetic defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked recessive (chromosome Xq28)</td>
</tr>
<tr>
<td>Autosomal dominant (vasopressin-neurophysin gene)</td>
</tr>
<tr>
<td>Autosomal recessive (Wolfram/DIDMOAD syndrome, chromosome 4p16)</td>
</tr>
</tbody>
</table>

* Adapted from Srivatsa et al (2007) and Robertson (2004).

### Table 2: Secondary Neurogenic Diabetes Insipidus*

<table>
<thead>
<tr>
<th>Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head injury</td>
</tr>
<tr>
<td>Transection of pituitary stalk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniopharyngioma</td>
</tr>
<tr>
<td>Germinoma</td>
</tr>
<tr>
<td>Pinealoma</td>
</tr>
<tr>
<td>Optic glioma</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Metastatic leukemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection (meningitis/encephalitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavernous sinus aneurysm</td>
</tr>
<tr>
<td>Hypoxic-ischemic injury</td>
</tr>
</tbody>
</table>

* Adapted from Srivatsa et al (2007) and Robertson (2004).

Nephrogenic DI is caused by the inability of the renal collecting ducts to absorb water in response to AVP. This renal resistance to AVP may be partial or total. Nephrogenic DI is classified as primary (genetic defect of renal AVP action) or secondary (acquired defect of renal AVP action). The feature that distinguishes nephrogenic DI from neurogenic DI is the plasma concentration of AVP. The AVP concentration in relation to the hydration status is low in neurogenic DI, while it is markedly raised in nephrogenic DI, especially in infants with total renal resistance to AVP. The primary cases of nephrogenic DI tend to be less common, but more severe and irreversible; the secondary cases of nephrogenic DI, in contrast, tend to be more common, but less severe and potentially reversible with removal of the offending cause. The causes of nephrogenic DI are summarized in Tables 3 and 4.

### Table 3: Primary Nephrogenic Diabetes Insipidus*

<table>
<thead>
<tr>
<th>Genetic defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked recessive (vasopressin receptor-2 gene)</td>
</tr>
<tr>
<td>Autosomal dominant (aquaporin-2 gene)</td>
</tr>
</tbody>
</table>

* Adapted from Srivatsa et al (2007) and Robertson (2004).
Autosomal recessive (aquaporin-2 gene)

* Adapted from Srivatsa et al (2007) and Robertson (2004).

### Table 4: Secondary Nephrogenic Diabetes Insipidus

<table>
<thead>
<tr>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
</tr>
<tr>
<td>Demeclocycline</td>
</tr>
<tr>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Foscarnet</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Methicillin</td>
</tr>
<tr>
<td>Ofloxacin</td>
</tr>
<tr>
<td>Rifampin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pyelonephritis</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
</tr>
</tbody>
</table>

| Polycystic/multicystic kidney |

* Adapted from Srivatsa et al (2007) and Robertson (2004).

Dipsogenic polyuric DI is a rare disorder, seen mostly in older adolescents and adults, characterized by compulsive water drinking in the absence of a physiologic stimulus to drink. This disorder may be a manifestation of a psychiatric illness (psychogenic polydipsia), result from an abnormal thirst perception from a hypothalamic defect (dipsogenic polydipsia), or be prompted by the advice of health care workers or the media regarding health benefits of water consumption (iatrogenic polydipsia). In neonates, excessive fluid administration, either from miscalculation or during fluid resuscitation, can potentially mimic dipsogenic polyuric DI.

The infant in this vignette does not have central nervous system features that suggest a neurogenic cause of DI, either primary or secondary. The delayed onset (6 weeks of postnatal age rather than shortly after birth) of the fluid-electrolyte imbalance, temporally related to the initiation of amphotericin B treatment for candidiasis, suggests an acquired (secondary) nephrogenic cause of DI. The fluid intake in the infant in this vignette is not excessive enough to warrant consideration of a dipsogenic polyuric cause of DI.

### References


### American Board of Pediatrics Content Specification(s)

Water/Salt/Renal: Know how to evaluate and manage inadequate or excessive water intake

Water/Salt/Renal: Know the specific hormonal factors that influence water balance in newborn infants

Water/Salt/Renal: Know the effects of arginine vasopressin (antidiuretic hormone) on sodium and water balance

Water/Salt/Renal: Know the etiology of electrolyte abnormalities in the neonate

Water/Salt/Renal: Recognize the clinical and laboratory manifestations of electrolyte abnormalities in the neonate
A 4-day-old male infant born at 41 weeks' gestation is readmitted with tonic-clonic seizures that are difficult to control, hiccups, and hypotonia. Despite phenobarbital and phenytoin treatment, overt seizures are occurring every 15 to 30 minutes. Hiccups occur frequently, and several self-resolved apnea episodes also have been observed. Electroencephalography revealed status epilepticus and a background burst-suppression pattern. Hiccups were noticed beginning on the first day after birth and the seizures were first noticed at 2 days of age.

The infant's mother is an 18-year-old primigravida. Although the prenatal course had been uncomplicated, an increase in fetal movement frequency was noticed in the week before birth. Furthermore, fetal movements were reported to be "jerky," erratic, a few minutes in duration, and recurring several times an hour.

Laboratory studies, blood and cerebral spinal fluid cultures (for bacteria, fungi, and viruses), and cerebrospinal fluid polymerase chain reaction for herpes virus have been normal for age. No acidosis or ketosis has been detected. The serum ammonia, lactate, and pyruvate concentrations are normal. Magnetic resonance imaging of the brain revealed mild thinning of the corpus callosum. Urine and plasma specimens have been sent for organic acid and amino acid screening.

Of the following, the compound responsible for the disorder in this infant MOST likely is:

A. glycine
B. leucine
C. methylmalonic acid
D. phenylalanine
E. pyridoxine

Neonates presenting in utero or in the first days after birth with seizures, tone abnormalities, and stupor may have one of many underlying disorders. Hypoxic-ischemic encephalopathy and anomalies, hemorrhage, and infection of the central nervous system account for most of these cases. Less frequent causes for this triad of symptoms are glucose, calcium and electrolyte imbalances, metabolic disturbances, and drug withdrawal.

Of the metabolic causes for seizures, tone abnormalities, and stupor, nonketotic hyperglycinemia (glycine encephalopathy) may be differentiated from other causes by:

- the presence of hiccups
- in utero presentation or onset of seizures within the first days after birth
- poor response to anticonvulsant medications
Disorders of protein metabolism (such as nonketotic hyperglycinemia, maple syrup urine disease, and phenylketonuria), organic acidemias (such as methylmalonic and propionic acidemias), urea cycle defects, and pyridoxine deficiency may present with seizures, tone abnormalities, and stupor in neonates (Table). Prenatal and perinatal history, physical examination, laboratory findings, electroencephalography, and magnetic resonance spectroscopy can narrow the differential diagnosis considerably.

### Table: Diagnostic Clues for Select Metabolic Disorders Causing Seizures, Tone Abnormalities, and Stupor

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical Onset</th>
<th>Response to Antiepileptics</th>
<th>Laboratory Abnormalities</th>
<th>Electroencephalography</th>
<th>Magnetic Resonance Imaging of the Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonketotic hyperglycinemia</td>
<td>In utero first days of age</td>
<td>Poor</td>
<td>Hyperglycinemia; elevated spinal fluid: plasma glycine</td>
<td>Burst-suppression</td>
<td>Glycine peak on long-echo spectroscopy</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>After 2 days of age</td>
<td>Unilateral</td>
<td>Ketonacidosis; hypoglycemia</td>
<td>Burst-suppression with 'comblike' pattern</td>
<td>Lactate, branch chain ketoacids abnormal</td>
</tr>
<tr>
<td>Methylmalonic acidemia</td>
<td>After 2 days of age</td>
<td>Unilateral</td>
<td>Metabolic acidosis; hyperammonemia; hyperglycinemia; cytopenias</td>
<td>Nonspecific</td>
<td>Globus pallidus particular abnormal</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>After 2 weeks of age</td>
<td>Unilateral</td>
<td>Elevated spinal fluid phenylalanine</td>
<td>Nonspecific</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Pyridoxine deficiency with seizures</td>
<td>In utero first days of age</td>
<td>Poor</td>
<td>Elevated spinal fluid glutamate and reduced y-aminobutyric acid</td>
<td>Generalized bursts of bilaterally synchronous high voltage rhythm with sharp and spike waves</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Nonketotic hyperglycinemia is a disorder of glycine metabolism causing glycine accumulation in all tissues, including the brain. Signs and symptoms most relate to toxicity of glycine in the brain (glycine encephalopathy). Although a number of variants exist, 85% of neonates with the disorder have the neonatal severe form that presents with the symptoms and findings seen in the infant in the vignette. Importantly, nonketotic hyperglycinemia becomes a diagnostic consideration when the most frequent causes for neonatal encephalopathy that present in the first hours to days after birth (hypoxic ischemic encephalopathy; anomalies, hemorrhage, or infection of the central nervous system; hypoglycemia; hypocalcemia) are excluded and hiccups, a relatively specific finding, are present.

Pyridoxine deficiency is a rare disorder that may present in the first hours after birth. Myoclonic seizures beginning in utero or hours to months after birth are the predominant finding in neonatal pyridoxine deficiency. On the other hand, the metabolic defects of the branched chain amino acids (maple syrup urine disease, an oxidative decarboxylation defect of leucine, isoleucine, and valine), phenylalanine, and fatty acid synthesis (methylmalonic acidemia or propionic acidemia, fatty acid synthetase defects) generally present 2 days or more after birth, after toxic metabolites accumulate. Symptoms often include jaw rigidity, dysphagia, bulging fontanel, ophthalmoplegias, and an odor resembling maple syrup, especially noted in cerumen, which denotes maple syrup urine disease. A pattern of vomiting, stupor, tachypnea, and seizures, which if untreated, leads to coma and death, suggests methylmalonic acidemia. Phenylketonuria, caused by a defect in phenylalanine hydroxylase, typically presents several weeks after birth with symptoms including vomiting, hypertonia, hyperactive deep tendon reflexes, light complexon, musty or mousy odor; seizures commonly present later in infancy.

Laboratory abnormalities such as hypoglycemia, acidosis, ketosis, hyperammonemia, and cytopenias are conspicuously absent in nonketotic hyperglycinemia. Maple syrup urine disease is caused by a defect in the oxidative decarboxylation of branched chain amino acids (maple syrup urine disease), and valine to short chain fatty acids. Accumulation of these ketoacids, especially of leucine (ketoisocaproic acid), results in ketoacidosis (large anion gap) and secondary hypoglycemia. Methylmalonic acidemia are caused by two defects in methylmalonyl-CoA mutase and three defects in vitamin B12 metabolism. Metabolic acidosis and secondary hyperammonemia (methylmalonyl-CoA inhibition of carbamyl phosphate synthase of the urea cycle) and hyperglycinemia (methylmalonyl-CoA inhibition of the glycine cleavage enzyme complex) characterize the metabolic defects in methylmalonic acidemia and propionic acidemia. This constellation of metabolic abnormalities is referred to as the "ketotic hyperglycinemia syndrome." Additional laboratory clues to defects in methylmalonic and propionic acid metabolism include neutropenia, anemia, and thrombocytopenia. Laboratory studies are frequently normal during the first days after birth in infants with phenylketonuria and pyridoxine-dependent seizures.

Electroencephalography may aid in differentiating causes for neonatal seizures. Nonketotic hyperglycinemia results in the accumulation of glycine, which has inhibitory (brain stem-associated apnea, hypotonia, weakness), excitatory (brainstem-associated hiccups, neuron-associated seizures, hyperexcitability,
myoclonus), and neurostructural (especially myelinization and neuronal development) effects. A burst-suppression pattern on encephalography characterizes nonketotic hyperglycinemia. In maple syrup urine disease, the electroencephalogram often shows a background burst-suppression pattern with a characteristic "comblike" pattern with bursts and runs of 5 to 7 Hz, primarily monophasic negative activity in the central and central-parasaggital regions of the brain. Electroencephalography does not have characteristic findings in patients with methylmalonic acidemia and in phenylketonuria. In pyridoxine dependency seizures, a unique electroencephalographic rhythm is composed of generalized bursts of bilaterally synchronous high-voltage (1-4 Hz) activity with intermixed sharp or spike waves. Although the clinical seizures may respond promptly to intravenous pyridoxine, the characteristic electrical pattern may not normalize for minutes to hours.

Magnetic resonance imaging of the brain is frequently a part of evaluations for neonatal seizures, tone abnormalities, and stupor. Absence or thinning of the corpus callosum, cerebral white matter abnormalities, and cortical atrophy are frequently found on magnetic resonance images in many metabolic disorders, including nonketotic hyperglycinemia, maple syrup urine disease, methylmalonic acidemia, phenylketonuria, and pyridoxine deficiency. On diffusion-weighted magnetic resonance imaging, increased signal is often present in the brain stem, cerebral peduncles, and posterior limbs of the internal capsule and consistent with a vacuolating myelinopathy. Magnetic resonance long-echo spectroscopy of the brain, however, may demonstrate specific metabolite peaks consistent with a specific disorder. For example, long-echo spectra may show elevation of glycine in the brain of infants with nonketotic hyperglycinemia.

References


American Board of Pediatrics Content Specification(s)

Endocrine/Metabolic/Thermal: Know the causes and differential diagnosis of metabolic encephalopathy

Endocrine/Metabolic/Thermal: Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids

Endocrine/Metabolic/Thermal: Know the clinical manifestations, laboratory features, and treatment of organic acid disorders

Endocrine/Metabolic/Thermal: Know the causes and management of metabolic encephalopathies in newborn infants

Neurology: Understand the differential diagnosis and evaluation of neonatal seizures
Question: 9

A 28-year-old obese woman with poorly controlled type I diabetes mellitus is planning to get pregnant. In addition to insulin, she takes supplemental iron, vitamin E, and prenatal vitamins. Her husband also has diabetes. She meets with an obstetrician to find out about her risk of having an infant with a major birth defect.

Of the following, this woman’s MOST significant risk factor for delivering an infant with a major birth defect involves:

- A. coexisting paternal diabetes
- B. glycemic control before conception
- C. glycemic control during pregnancy
- D. increased vitamin E intake
- E. maternal obesity

Correct

Women with diabetes mellitus (DM) during pregnancy can be classified by their age at diabetes onset and severity of disease (Table).

<table>
<thead>
<tr>
<th>Class</th>
<th>Onset of Diabetes Mellitus</th>
<th>Vascular Disease</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Gestational</td>
<td>None</td>
<td>No insulin, diet-controlled</td>
</tr>
<tr>
<td>A2</td>
<td>Gestational</td>
<td>None</td>
<td>Small amount of insulin</td>
</tr>
<tr>
<td>B</td>
<td>&gt;20 years old or duration &lt;10 years</td>
<td>None</td>
<td>Insulin-dependent</td>
</tr>
<tr>
<td>C</td>
<td>10-19 years old or duration of 10-19 years</td>
<td>None</td>
<td>Insulin-dependent</td>
</tr>
<tr>
<td>D</td>
<td>&lt; 10 years old or duration over 20 years</td>
<td>Mild retinopathy</td>
<td>Insulin-dependent</td>
</tr>
<tr>
<td>E</td>
<td>Any age</td>
<td>Nephropathy</td>
<td>Insulin-dependent</td>
</tr>
<tr>
<td>R</td>
<td>Any age</td>
<td>Proliferative retinopathy</td>
<td>Insulin-dependent</td>
</tr>
<tr>
<td>G</td>
<td>Any age</td>
<td>Many pregnancy failures</td>
<td>Insulin-dependent</td>
</tr>
<tr>
<td>H</td>
<td>Any age</td>
<td>Heart disease</td>
<td>Insulin-dependent</td>
</tr>
<tr>
<td>I</td>
<td>Any age</td>
<td>Prior renal transplantation</td>
<td>Insulin-dependent</td>
</tr>
</tbody>
</table>

* Adapted from Cunningham and colleagues (2001).

Gestational diabetes, defined as glucose intolerance diagnosed during pregnancy, accounts for 90% of cases of DM in pregnancy; adult-onset or type 2 DM with insulin-resistance accounts for 8% of cases and type 1 DM accounts for the remaining 1% to 2% of cases. Although women with gestational diabetes are not at risk
of having an infant with congenital anomalies, women with prepregnancy DM or DM early in pregnancy have a greater risk of having an infant with birth defects. Two-thirds of the congenital anomalies associated with DM involve:

- cardiovascular system (eg, structural heart defects)
- central nervous system (eg, spina bifida, hydrocephaly, anencephaly)
- genitourinary system (eg, renal agenesis, cystic renal disease, duplex ureter)
- gastrointestinal system (eg, situs inversus, anal/rectal atresia)
- skeletal anomalies (eg, caudal regression syndrome)

Maternal diabetes is not associated with a greater risk of fetal chromosomal abnormalities.

Major birth defects occur in 1% to 2% of the general population and this anomaly risk increases four- to eightfold in diabetic women who had suboptimal glycemic control before conception. Women with type 1 DM have a 5% to 10% risk of having a child with a major malformation. Aggressive preconception and first-trimester glycemic control in women with prepregnancy DM has been shown to decrease the anomaly rate by 50% to 75% in some studies and to general population levels in other studies. Because a pregnancy is not always planned, women of child-bearing age with DM should achieve strict euglycemia to minimize the risk of having a child with a congenital anomaly.

Studies have not shown an effect of coexisting paternal diabetes on the risk of fetal anomalies. The intrauterine environment plays more of a role in anomaly risk than paternal factors. However, the infant has an increased risk of developing diabetes later in life if the father has DM.

Women with poor glycemic control in the periconceptional period, evident by having a glycosylated hemoglobin (HbA1C) value greater than 8.5%, are at higher risk of having an infant with a congenital anomaly. In one study, women with an HbA1C value greater than 8.5% during the periconceptional period had a 22.4% rate of fetal malformation compared with a 3.4% rate in women with an HbA1C value less than 8.5%. As reported in another study, if the preconception HbA1C value was less than 7%, the risk of delivering an infant with a major birth defect was comparable to that of a healthy female population. The risk of malformation correlates directly with the prepregnancy glycohemoglobin value. Thus the woman in this vignette would have a low risk of having an infant with a congenital anomaly if her HbA1C value was less than 8.5%.

Animal studies are beginning to elucidate potential molecular mechanisms that might explain how DM affects embryogenesis. Administering antioxidants, such as vitamin E and lipoic acid, to diabetic rats prevents the development of fetal malformations. One potential hypothesis for this finding is that hyperglycemia increases oxidative free radicals that are embryotoxic, and this toxicity can be inhibited by antioxidants. Thus, it is unlikely that increased vitamin E intake raises the congenital anomaly risk for the woman in this vignette. Further investigations are needed to elucidate the precise pathway for anomaly formation in children born to women with prepregnancy DM.

Maternal obesity, common in women with type 2 DM, has been shown to double the risk of having an infant with macrosomia. This association may explain the inability to completely prevent fetal macrosomia in diabetic women with good glycemic control. Furthermore, if pregnant women with gestational DM gain more weight during pregnancy than the weight-gain recommendations advocated by the Institute of Medicine, they are at greater risk of having a preterm delivery, primary cesarean delivery, and infant with macrosomia. The degree of maternal obesity in women with prepregnancy DM does not correlate with the incidence of congenital birth defects.

In addition to poor periconceptional glycemic control and elevated HbA1C values, Lucas and associates also found an association between malformations and the duration of DM and extent of vascular disease. They reported that most fetal anomalies occur in women with greater severity of illness (ie, pregnant women with class C, D, F, H, and R diabetes).

References


Matern Fetal Med. 2000;9:14-20

American Board of Pediatrics Content Specification(s)
Maternal-Fetal Medicine: Know the effects on the fetus and/or newborn infant of maternal diabetes mellitus (including gestational diabetes) and their management
A 2-day-old term male infant develops vomiting, unresponsiveness, seizures, and tachypnea. The prenatal course was uncomplicated and he was delivered vaginally. His mother had had a previous male child who had died suddenly 3 days after birth presumably from sepsis; no autopsy or additional studies had been performed. The infant's three sisters are healthy. He has been evaluated for sepsis and meningitis, with cultures, white blood cell counts, and chemistries of the cerebrospinal fluid being normal. Computed tomography of the brain demonstrates cerebral edema. Laboratory studies are as follows:

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Conventional (SI) Unit</th>
<th>Patient Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate, mEq/L (mmol/L)</td>
<td>19 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anion gap, mEq/L (mmol/L)</td>
<td>12 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum urea nitrogen, mg/dL (mmol/L)</td>
<td>1.36 (1.36)</td>
<td>8-23 (2.9-8.2)</td>
<td></td>
</tr>
<tr>
<td>Ammonia, μg/dL (μmol/L)</td>
<td>1,175 (690)</td>
<td>36-162 (21-95)</td>
<td></td>
</tr>
<tr>
<td>Lactate, mg/dL (mmol/L)</td>
<td>13.5 (1.5)</td>
<td>10-21 (1.0-2.3)</td>
<td></td>
</tr>
<tr>
<td>Pyruvate, μg/dL (μmol/L)</td>
<td>0.05 (0.06)</td>
<td>0.44 – 1.11 (0.05-0.12)</td>
<td></td>
</tr>
<tr>
<td>Citrulline</td>
<td>Trace</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orotic acid (urine), mg/g (mmol/mol)</td>
<td>14.6 (10.6)</td>
<td>1.9-7.3 (1.4-5.3)</td>
<td></td>
</tr>
</tbody>
</table>

Of the following, the treatment MOST efficient in reducing the symptoms in this infant is:

- A. amino acids
- B. benzoate
- C. exchange transfusion
- D. hemodialysis
- E. valproic acid

Incorrect
Correct Answer: D

Urea cycle defects are a major cause for hyperammonemia presenting in neonates, and should be considered whenever hyperammonemia is not accompanied by metabolic acidosis. The prevalence of this group of disorders is 1 in 30,000 live births. Ornithine transcarbamylase (OTC) deficiency accounts for 55% to 60% of urea cycle defect cases presenting during the neonatal period. Although most of the urea cycle defects are associated with an autosomal recessive inheritance pattern, OTC deficiency is inherited as an X-linked recessive disorder (OTC gene is located at Xp21.1). The infant in the vignette presented with classic symptoms associated with ammonia-induced neuronal toxicity. The family history,
respiratory alkalosis, low blood urea nitrogen, low concentration of plasma citrulline, and high concentration of urinary orotic acid are consistent with OTC deficiency (Figure). The primary goal of treatment is to reduce the concentration of ammonia as quickly as possible, for which hemodialysis is the preferred treatment.

Figure: Nitrogen excretion pathways and ornithine transcarbamylase deficiency. Low plasma citrulline and elevated urine orotic acid concentrations are indicative of ornithine transcarbamylase deficiency. (Adapted from Volpe JJ [2008].)

Ammonia concentrations are higher in the brain than in the blood because the only urea cycle enzyme present in significant quantities in the brain is argininosuccinic acid synthetase (responsible for converting citrulline to argininosuccinic acid) (Figure). In the brain, ammonia must be eliminated by other pathways, such as diffusion and conversion to glutamine. Glutamine is eliminated by diffusion and also via a glutamine-tryptophan transporter. The net result is glutamine efflux and tryptophan influx into the brain. The liver is the only organ that is quantitatively important for conversion of ammonia to urea. Hepatic conversion of ammonia to urea, therefore, is necessary to drive the diffusion gradient to move ammonia from other locations in the body.

Although the mechanism of brain injury from ammonia remains to be fully elucidated, several adverse biochemical effects associated with increased glutamine synthesis likely occur simultaneously:

- Elevated neuronal glutamine is directly toxic to neurons and induces stupor or coma.
- Tryptophan resulting from increased glutamine-tryptophan exchange during hyperammonemia is metabolized to serotonin and quinolinic acid, a neurotoxin. Quinolinic acid activates the N-methyl D-aspartate (NMDA) type of glutamate receptor and causes neuronal injury by (1) inducing an influx of sodium and water, swelling and lysis, and (2) by an influx of calcium with generation of cytotoxic free radicals. These mechanisms of cell death together are termed “excitotoxic neuronal death.”
- Astrocyte and oligodendrocyte edema also occurs with elevated intracellular glutamine concentrations. Swelling impairs the microcirculation and may result in ischemic injury.

There is currently no cure for OTC deficiency or other urea cycle defects. Liver transplantation in early infancy is a promising option. Aggressive medical treatment generally is directed at controlling ammonia concentrations in the body and avoiding catabolic states, and includes the following measures:

- **Management of hyperammonemia.**
  - Hemodialysis is the most rapid method of ammonia elimination. In neonates, hemodialysis is associated with difficulties with vascular access but is possible using extracorporeal circulation. Modalities for treatment of hyperammonemia such as hemofiltration and peritoneal dialysis are slower and less efficient than pump-driven hemodialysis. Exchange transfusion is of limited usefulness.
  - Alternate pathways of ammonia removal can be helpful to reduce ammonia concentrations. Sodium benzoate and glycine (derived from ammonia and bicarbonate) form hippurate that is nontoxic and easily excreted. Sodium phenylacetate (or phenylbutyrate) and glutamine derived from ammonia form phenylacetylglutamine, also nontoxic and readily excreted in the urine. Citrulline supplementation may drive the urea cycle to form urea if some residual OTC activity is present. Valproic acid antagonizes the effects of sodium benzoate and sodium phenylacetate so its use for seizure management should be avoided during treatment for hyperammonemia. Arginine infusion can be helpful to stimulate ammonia removal in cases of argininosuccinase deficiency and may be considered prior to initiating hemodialysis.
  - Protein elimination or restriction for 24 to 48 hours in acutely ill infants helps reduce ammonia production. Caloric needs are initially provided by carbohydrate and fat, either enteral or parenteral depending on gastrointestinal function and clinical status. Amino acid and protein supplementation are withheld when infants with OTC deficiency are acutely ill. Following this short
period of protein elimination, limited protein intake is resumed with the goals of preventing
catabolism and providing adequate protein for growth. Fluid volume is restricted to minimize brain
edema.

- Prevention of catabolism
  - Catabolism can be reduced by limiting protein intake (1.0 to 1.5 g/kg per day) and supplying calories with glucose and fat. Avoidance of prolonged fasting or starvation also helps prevent hyperammonemia in infants with OTC deficiency. Similarly, catabolism can be controlled by avoiding intravenous corticosteroids and large boluses of protein or amino acids.
  - Childhood illnesses or injuries may exacerbate symptoms in children with OTC deficiency. Careful handwashing, complying with immunizations, supplementing with vitamins and fluoride, and adhering to child safety recommendations should be encouraged. Close monitoring of ammonia is recommended if childhood illnesses occur and when there is physical injury or trauma.
  - Making the transition from parenteral to enteral feedings as soon as possible helps maintain gastrointestinal homeostasis and reduce catabolism.

References


American Board of Pediatrics Content Specification(s)

Endocrine/Metabolic/Thermal: Know the causes and differential diagnosis of metabolic encephalopathy

Endocrine/Metabolic/Thermal: Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle

Neurology: Know the causes and management of metabolic encephalopathies in newborn infants
Figure: Summary of vitamin D metabolism. Vit D₃ = vitamin D₃; 25 D₃ = 25(OH) vitamin D₃; 1,25 D₃ = 1,25(OH)₂vitamin D₃; PTH = parathyroid hormone; X-hypophos rickets = X-linked hypophosphatemic rickets; Pseudo Vit D deficiency = pseudo–vitamin D deficiency; Vit D resistance = vitamin D-resistant rickets.

- low Ca⁺⁺
- low phosphate
- high PTH

Vit D₃

25 D₃

1,25 D₃ (calcitriol)

- anticonvulsants
- liver disease

- renal disease
- X-hypophos rickets
- pseudo Vit D deficiency

Vit D resistance

- Gut Ca⁺⁺ & PO₄ absorption

Bone deposition
**Question: 1**

A 2-month-old infant is brought by his foster mother to your university's pediatric clinic. He was born at 34 weeks' gestation in another state, and this is his first visit since being discharged to foster care; he was given full-term infant formula with iron. The clinic resident has seen the infant, and reports to you that the infant has thickening at the wrists, craniotabes, costochondral beading, a Harrison groove, and some muscle weakness. Also, the infant has no hair. On close questioning of the foster mother, you find out that the biologic mother once told her that two of this child's six siblings also have no hair, and must take special pills.

Of the following, the metabolic bone disease MOST likely to be affecting this infant is:

- A. dietary deficiency of vitamin D
- B. hypophosphatasia
- C. pseudo–vitamin D deficiency
- D. vitamin D–resistant rickets
- E. X-linked hypophosphatemia

**Incorrect**

Correct Answer: D

Diseases of bone metabolism may be acquired, as in dietary deficiency of vitamin D, or may be hereditary, as in the other diseases listed in the vignette. Diseases of bone metabolism may manifest in the neonatal period, or may be silent until later in infancy. If the cause is hereditary, clues in the family history may help discern the specific condition and prepare for the needed treatments. Familial short stature, leg deformities, difficulties with walking, or unexplained death in infancy may be important findings from the family history. Of the conditions in the vignette, the one most likely to involve familial alopecia in affected siblings is vitamin D-resistant rickets.

The manufacturing of bone involves an organic phase and a mineral phase. The organic osteoid is formed first, and then calcium and phosphate are intercalated. Any interference with the mineral phase results in osteomalacia in an adult or rickets in a child. The undermineralized osteoid is weaker than fully formed bone, and so is prone to deformities such as bowing of the long bones and widening, fraying, and cupping of the metaphyses. Craniotabes, costochondral beading, Harrison groove, and muscle weakness may also be consequences of undermineralized bone.

Mineral deficits can directly interfere with the mineral phase, such as X-linked hypophosphatemic rickets. Hypophosphatasia interferes with the proper handling of
phosphate. Vitamin D is involved in many of the other hereditary bone diseases.

The Figure summarizes vitamin D metabolism. Vitamin D₃ is synthesized in the skin or absorbed from the gut. It is converted in the liver to 25(OH) vitamin D₃, a process that is decreased by anticonvulsants or severe liver disease. In the kidney, 25(OH) vitamin D₃ is converted to 1,25(OH)₂ vitamin D₃, also known as calcitriol. This process is reduced in the face of renal disease, hypophosphatemic rickets, or pseudo–vitamin D deficiency; and increased in the presence of hypocalcemia, hypophosphatemia, or hyperparathyroidism. Calcitriol, the most biologically active metabolite of vitamin D, acts on the gut to promote calcium and phosphorus absorption, and on the bone to regulate both deposition and resorption of calcium. The action of calcitriol is blocked in vitamin D-resistant rickets.

The child in the vignette is at risk for hereditary resistance to vitamin D, also known as vitamin D-dependent rickets type II. It is an autosomal recessive disease resulting from an abnormality in the end-organ receptor for calcitriol. Neonatal symptoms may include hypocalcemia, early-onset rickets, and alopecia. Approximately 50% to 70% of infants with vitamin D-resistant rickets have alopecia, which ranges from alopecia areata to alopecia totalis. Vitamin D-resistant rickets is refractory to high doses of vitamin D, especially if alopecia is present. Treatment with high doses of calcium and phosphate allows slow improvement in bone mineralization. Alopecia is not correctable.

Pseudo–vitamin D deficiency, also known as vitamin D-dependent rickets type I, is an autosomal recessive deficiency of 1α-hydroxylase. In the kidneys, this enzyme is responsible for the conversion of 25(OH) vitamin D₃ to calcitriol. Deficiency of the enzyme causes muscle weakness at birth and rickets in the first year after birth. Growth retardation or hypocalcemic seizures may also be seen. Treatment is with oral calcitriol. Alopecia is not a feature.

X-linked hypophosphatemia is caused by a defect in phosphate transport in the kidney. Decreased renal tubular reabsorption of phosphate results in a low serum phosphate concentration. Rickets and poor linear growth are seen in the first year, with delayed dentition and tooth abscesses in later years. In addition, 1α-hydroxylase activity in the kidney is often affected, necessitating calcitriol treatment as well as phosphate replacement. Female carriers often exhibit milder forms of the disorder, and may present only with short stature.

Hypophosphatasia is caused by autosomal recessive mutations of the tissue-nonspecific isoenzyme of alkaline phosphatase. Chondrocyte handling of phosphorus is impaired, resulting in poor mineralization of bones. Long bones are short, bowed, and have a moth-eaten appearance on radiography. Premature tooth loss is seen because of poor dental cementum. Hypophosphatasia has several phenotypes, ranging in severity from in utero death, because of skeletal deformities, to mild adult-onset osteomalacia. Presentation in the neonate is often severe, with death occurring from fail chest, pneumonia, or renal failure caused by nephrocalcinosis secondary to hypercalcaemia and hypercalciuria. Onset in later childhood is often followed by spontaneous recovery. Temporary improvement is seen with infusion of alkaline-phosphatase-rich plasma. Bone marrow transplantation has been successful in a few patients.

Dietary deficiency of vitamin D is not hereditary, but members of a family may share dietary habits and activity patterns that result in siblings having similar nutritional deficiencies. Alopecia is not a feature of dietary deficiency of vitamin D.

**Suggested Readings**

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**American Board of Pediatrics Content Specification(s)**

Endocrine/Metabolic/Thermal: Know the interrelated effects of various hormones, including parathormone, calcitonin, and vitamin D on calcium, phosphorus, and magnesium metabolism in the fetus and neonate.
Question 8

An infant born at 36 weeks’ gestation weighs 3,200 g and his crown-heel length is 38 cm. He is vigorous at birth. After skin-to-skin contact with his mother and a short time on the breast he appears normal. The plasma glucose concentration is 30 mg/dL (1.67 mmol/L) 2 hours after birth, 30 minutes after breastfeeding.

Of the following, the MOST appropriate intervention for this infant is:

- A. breastfeeding
- B. formula feeding
- C. glucagon injection
- D. intravenous glucose infusion
- E. oral glucose administration

Correct

After birth, all infants must adapt to being separated from a continuous source of nutrients, including glucose. Physiologically, the blood glucose drops transiently and asymptotically to concentrations as low as 30 mg/dL (1.67 mmol/L). Then in response to intake of glucose and other nutrients, gluconeogenesis, and glycogenolysis, the blood glucose rises to concentrations at or above 45 mg/dL (2.5 mmol/L) by 12 hours after birth. During this physiologic nadir, infants release ketone bodies from fat to produce fuel. Breastfed infants have lower glucose concentrations and higher concentrations of ketone bodies than formula-fed infants. Appropriately grown full-term
infants born to healthy mothers after an uncomplicated pregnancy are at low risk for hypoglycemia, and routine screening of this population is not recommended.

Neonatal hypoglycemia is a concern among infant populations at risk for a profound and/or prolonged period of subnormal blood glucose concentration because of associations with both short-term symptoms and long-term sequelae. The overall risk for (symptomatic) neonatal hypoglycemia is estimated at 1 to 3 per 1,000 live births. The risk is inversely related to gestational age.

Low blood glucose concentrations accompany conditions associated with impaired gluconeogenesis or ketogenesis, as may occur with hyperinsulinemia; abnormal counter-regulatory hormone function; reduced substrate supply; or fatty-acid oxidation disorders. Low blood glucose concentrations also occur more frequently among infants who present with most of the conditions leading to admission to intensive care. Blood glucose concentrations are often assessed in these conditions because symptoms of low blood glucose are nonspecific, risk is high, and treatment is available to prevent sequelae.

Clinical or symptomatic hypoglycemia presents with a wide range of nonspecific symptoms, both generalized and neurologic (Table). To attribute more subtle symptoms to hypoglycemia, the following triad (Whipple triad) should be fulfilled:

- low blood glucose concentration
- sign(s) consistent with hypoglycemia (Table)
- resolution of symptoms after normalization of blood glucose concentration

The more serious symptoms of seizures and coma generally follow either profound (blood glucose concentration <10 mg/dL [0.56 mmol/L]) or repetitive episodes of hypoglycemia. Because these symptoms tend to appear after protracted hypoglycemia and brain injury, they may not easily or quickly resolve as the blood sugar is normalized and the brain recovers. It is generally recommended that the symptomatic infant with blood glucose concentration less than 40 mg/dL [2.2 mmol/L] receive intravenous glucose with a therapeutic goal of reaching and maintaining blood glucose concentration between 40 and 50 mg/dL (2.2-2.8 mmol/L). Higher concentrations are not targeted in the presence of hyperinsulinemia because insulin secretion is stimulated at higher glucose concentrations.

The question of screening neonates for low blood glucose concentrations has confounded neonatologists and pediatricians. Most experts now agree that universal screening is neither practical nor needed. Screening for hypoglycemia is appropriate for asymptomatic infants who are small for gestational age (substrate deficiency), born to diabetic mothers (hyperinsulinemia), late preterm (substrate deficiency), and large for gestational age (possible hyperinsulinemia). The rationale for screening is to detect low concentrations of glucose before they are either low enough or sufficiently prolonged to cause neurologic damage. Thus, screening the infant in the vignette was consistent with current recommendations by virtue of his being born late preterm.

The care of infants in the at-risk categories is illustrated in the Figure. Symptomatic infants are treated. To allow for the physiologic nadir among asymptomatic infants, the immediate postdelivery period is divided: birth to 4 hours’ age, and 4 hours to 24 hours’ age. Intravenous glucose is recommended to be reserved for infants with screening blood glucose values less than 25 mg/dL (1.4 mmol/L) and less than 35 mg/dL (1.9 mmol/L), respectively, and for those infants whose preprandial values are less than 45 mg/dL (2.5 mmol/L) after refeeding. Infants with screening values of 45 mg/dL or more are followed according to their specific risk pattern. Small-for-gestational age and hyperinsulinemic infants may develop hypoglycemia up to 10 days after birth, whereas late preterm infants generally remain euglycemic once they show no preprandial concentrations less than 45 mg/dL (2.5 mmol/L) for three consecutive feedings.
The infant in the vignette presented in the late preterm interval. His weight and length are at the 50th percentile for 36 weeks’ gestational age, and the maternal history presents no added risks. According to the recommended strategy, refeeding (breastfeeding) and retesting would be the next step for this infant.

Breastfed infants should return to the breast rather than receive supplementation with either formula or oral glucose; this is especially true of 5% dextrose, with only 17 calories per 100 mL. Intravenous glucose is not recommended at this stage, nor is glucagon.

**Suggested Readings**


McGowan JE. Neonatal hypoglycemia: fifty years later, the questions remain the same. *NeoReviews*. 2004;5:e363-e364. Accessed March 25, 2011 at: [http://neoreviews.aappublications.org/cgi/content/full/5/9/e363](http://neoreviews.aappublications.org/cgi/content/full/5/9/e363)

**American Board of Pediatrics Content Specification(s)**

Endocrine/Metabolic/Thermal: Know the causes (including hyperinsulinemic hypoglycemia) of neonatal hypoglycemia syndromes

Endocrine/Metabolic/Thermal: Recognize the clinical and laboratory features of neonatal hypoglycemia

Endocrine/Metabolic/Thermal: Recognize the approach to therapy and prevention of neonatal hypoglycemia

Endocrine/Metabolic/Thermal: Know the potential sequelae of neonatal hypoglycemia
**Question: 8**

An infant born at 36 weeks’ gestation weighs 3,200 g and his crown-heel length is 38 cm. He is vigorous at birth. After skin-to-skin contact with his mother and a short time on the breast he appears normal. The plasma glucose concentration is 30 mg/dL (1.67 mmol/L) 2 hours after birth, 30 minutes after breastfeeding.

Of the following, the MOST appropriate intervention for this infant is:

- A. breastfeeding
- B. formula feeding
- C. glucagon injection
- D. intravenous glucose infusion
**Figure:** Screening for and management of postnatal glucose homeostasis in late-preterm (LPT; 34-36 6/7 weeks) and full-term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants. (From American Academy of Pediatrics Committee on Fetus and Newborn [2011].)

<table>
<thead>
<tr>
<th>Symptomatic and &lt;40 mg/dL</th>
<th>IV glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth to 4 hours of age</strong></td>
<td><strong>4 to 24 hours of age</strong></td>
</tr>
<tr>
<td>INITIAL FEED WITHIN 1 hour</td>
<td>Continue feeds q2-3 hours</td>
</tr>
<tr>
<td>Screen glucose 30 minutes after 1st feed</td>
<td>Screen glucose prior to each feed</td>
</tr>
<tr>
<td>Initial screen &lt;25 mg/dL</td>
<td>Screen &lt;35 mg/dL</td>
</tr>
<tr>
<td>Feed and check in 1 hour</td>
<td>Feed and check in 1 hour</td>
</tr>
<tr>
<td>&lt;25 mg/dL</td>
<td>25–40 mg/dL</td>
</tr>
<tr>
<td>IV glucose*</td>
<td>Refeed/IV glucose* as needed</td>
</tr>
<tr>
<td>25–40 mg/dL</td>
<td>&lt;35 mg/dL</td>
</tr>
<tr>
<td>IV glucose*</td>
<td>Refeed/IV glucose* as needed</td>
</tr>
<tr>
<td>35–45 mg/dL</td>
<td>35–45 mg/dL</td>
</tr>
</tbody>
</table>

Target glucose screen ≥45 mg/dL prior to routine feeds

*Glucose dose = 200 mg/kg (dextrose 10% at 2 mL/kg) and/or IV infusion at 5–6 mg/kg per min (80–100 mL/kg per d). Achieve plasma glucose level of 40–50 mg/dL.

Symptoms of hypoglycemia include: irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.

**Question: 8**

An infant born at 36 weeks’ gestation weighs 3,200 g and his crown-heel length is 38 cm. He...