Recent discoveries in fields such as genetics and cell biology have simultaneously advanced our understanding of endocrine disorders. Endocrine processes are fundamental to growth and development of the fetus and newborn. Prompt recognition of endocrine disorders in the neonate is the chief prerequisite to our ability to institute life-saving treatment and minimize long-term morbidity. This chapter will provide an overview of the clinical endocrine disorders that may be seen in the neonatal period.

THE ENDOCRINE SYSTEM
The word endocrine, from the Greek words endo (within) and kinein (to separate), describes a diverse group of ductless organs that secrete hormones directly into the bloodstream. The classic endocrine glands are the hypothalamus, pineal, pituitary, thyroid, parathyroid, thymus, pancreatic islet cells, adrenals, ovaries, and testes. Among the many roles of the endocrine system are coordination and regulation of metabolism, growth and development, and reproduction. In controlling body homeostasis, the endocrine and central nervous systems are intimately linked, forming the neuroendocrine system.

The endocrine glands are those that synthesize, store, and secrete hormones. Hormones are the chemical messengers, or signals, of the endocrine system. Secreted into the blood or extracellular fluid, hormones exert their actions on specific cells, usually in distant tissues, called target cells. Target cells respond to certain hormones because they contain receptors for those precise hormones. Hormones must first bind to these receptor sites before exerting physiologic actions. Some hormones, such as insulin, are fully active on release into the circulatory system, whereas others, such as T₄, require activation to produce their biologic effects (Kronenberg et al, 2003).

Many hormones are insoluble in water and must be bound to proteins to be transported in the circulatory system. These protein-bound hormones exist in rapid equilibrium with minute quantities of hormone that remain in the aqueous plasma. It is this “free” fraction of the circulating hormone that is taken up by the cell and represents the active hormone concentration.

Target hormone levels also serve as powerful negative feedback regulators of their own production via suppression of trophic hormones and hypothalamic releasing hormones. As the target hormone level rises, a message is sent to the anterior pituitary to reduce production of the respective trophic hormone, and also to the hypothalamus to reduce production of the respective releasing hormone. Endocrine disease can be caused by hormone overproduction, hormone underproduction, or altered tissue responses to hormones (Kronenberg et al, 2003).

Fetal Origins of Adult Disease
The intrauterine endocrine milieu can have powerful effects on growth and development of the fetal endocrine system. When exposed to a variety of different stressors (maternal undernutrition, uteroplacental insufficiency, or psychologic stress) the fetus releases glucocorticoids and catecholamines that, during critical periods of development, affect the development of the fetal hypothalamic-pituitary-adrenal axis. Chronic stress can also induce intrauterine growth restriction, or the so-called thrifty phenotype, in the fetus, an adaptation to the limited supply of nutrients. The way in which the fetus adapts is believed to permanently alter its physiologic and metabolic, a concept known as programming. Permanent alterations in fetal metabolic programming contribute to endocrine, metabolic, and cardiovascular disease in adult life (Fowden & Forhead, 2004).

Neonatal Endocrine Disorders
Endocrinopathy in the newborn can be caused by a mutation in a single gene or by genomic imprinting, when the expression of the gene depends on which parent passed on that particular gene (Rubin, 2004). In addition to well-described neonatal endocrine disorders such as hypothyroidism and congenital adrenal hyperplasia, endocrine dysfunction can affect the preterm infant in a variety of ways as a function of maturation. Endocrinopathy is associated with a number of chromosomal anomalies that present in the newborn period, including Down syndrome and Prader-Willi syndrome. Finally, there is the question of potentially disruptive effects of agents in the environment on the development of the endocrine system (Rubin, 2004). Numerous chemicals have known estrogenic or antiandrogenic properties and have been shown to disturb sexual differentiation in animals (Toppari, 2002). It is not known to what extent these agents are responsible for increases in hypospadias and testicular dysgenesis syndrome that have been reported in some parts of the world.
PITUITARY GLAND AND HYPOTHALAMUS
The pituitary gland has two distinct structures, the anterior and posterior pituitary, with different embryologic origins. The anterior pituitary develops from oral ectoderm, a diverticulum called Rathke’s pouch, and its cells differentiate into specific hormone-secreting cells. The posterior pituitary develops from neuroectoderm evaginating ventrally from the developing brain. The two tissues grow together into a single gland but remain functionally separate.

The hypothalamus, located just above the pituitary gland, secretes the releasing and inhibiting hormones that in turn influence the production of anterior pituitary hormones. Hypothalamic hormones are carried to the anterior pituitary via hypothalamic-hypophyseal portal veins where they bind to receptors on the anterior pituitary cells. Hormones produced by the anterior pituitary include growth hormone, prolactin, adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Hormones secreted by the posterior pituitary include oxytocin and hypothalamic-produced vasoressin (antidiuretic hormone, ADH). The hypothalamus is the interface between the endocrine and autonomic nervous systems (Rubin, 2004).

Disorders of the Anterior Pituitary
Congenital Hypopituitarism
Congenital hypopituitarism, though rare in the newborn, has a number of possible etiologies. Some cases of congenital hypopituitarism are attributed to mutations in genes encoding transcription factors involved in pituitary gland development (Palma Sisto, 2004). Congenital hypopituitarism can be caused by malformations including holoprosencephaly, septo-optic dysplasia, and other midline cerebral anomalies, the same developmental defects of the embryonic brain that lead to hypothyroidism and hypothalamic dysfunction. Infection and hypovolemic shock stemming from birth-related complications such as placenta previa and abruptio placentae are additional etiologies (Geffner, 2002).

Pathophysiology. Complete absence of the pituitary gland (pituitary agenesis) and other pituitary lesions can produce deficiencies of one or all pituitary hormones.

Panhypopituitarism is a deficiency of all pituitary hormones. In the newborn, the foremost effect of congenital hypopituitarism is hypoglycemia. Owing to the absence of growth hormone, and possibly cortisol as well, insulin acts in an unopposed manner, placing the neonate at risk for hypoglycemia (Geffner, 2002). In males, hypopituitarism can cause micropenis. Deficiency of growth hormone, and often gonadotropin, combine to stunt penile growth in utero; this is usually referred to as hypogonadotropic hypogonadism. Although fetal pituitary growth hormone is not the primary stimulus for fetal growth, growth hormone does make an important contribution to birth size.

Clinical Manifestations. Neonates may present with midline craniofacial defects such as cleft lip, cleft palate, or bifid uvula. Males may have a micropenis, defined as a normally formed and proportioned penis with a stretched penile length more than 2 SDs below the mean for age. Average penile length for preterm infants 30 weeks of age or older is 2.5 ± 0.4 cm and for term infants 3.5 ± 0.4 cm. For preterm infants 24 to 26 weeks’ gestation, the following formula can be used: penile length in centimeters = 2.27 + 0.16 × (gestational age in weeks) (Tuladhar et al, 1998). Hypoglycemia can be mild or severe and persistent. Later in the neonatal period infants may present with prolonged jaundice and direct hyperbilirubinemias, or evidence of other endocrinopathies, such as diabetes insipidus (high urine output, dehydration, hypernatremia).

Diagnosis. A pediatric endocrinologist usually coordinates the diagnostic testing and interpretation for these infants. The aim of laboratory testing is to determine which hormone deficiencies are present. Measurement of growth hormone, thyroid hormone, and cortisol are essential. Magnetic resonance imaging (MRI) of the brain is used to define the anatomy and look for a structural cause of hypopituitarism. For infants with suspected septo-optic dysplasia, an ophthalmologic examination is indicated.

Collaborative Management. The immediate goals of management are to stabilize the neonate’s blood sugar and ensure that the neonate is not at risk of life-threatening cortisol insufficiency. Hypoglycemia may not resolve without growth hormone replacement. Further treatment is geared toward correcting specific hormonal deficiencies (Palma Sisto, 2004). The infant will require follow-up management by the pediatric endocrinologist throughout hospitalization and after discharge.

Disorders of the Posterior Pituitary
Diabetes Insipidus
Diabetes insipidus (DI) is a deficiency of antidiuretic hormone (vasopressin). In neonates, central or neurogenic DI can be associated with congenital midline anatomic defects (septo-optic dysplasia, holoprosencephaly), central nervous system injury such as intracranial hemorrhage or hypoxia, neoplasms, or it can be idiopathic (Saborio et al, 2000).

Pathophysiology. Normally, ADH secretion is triggered by changes in osmolality detected by supraoptic and paraventricular osmosensors in the brain. Increased osmolality stimulates the posterior pituitary to release ADH, which in turn increases the permeability of the renal collecting tubules to water, reducing urinary water loss. Damage to the osmosensors, the posterior pituitary gland, or the hypothalamic-hypophyseal axis results in a deficiency of ADH and increased urinary free water loss.

Clinical Manifestations. Neonates with diabetes insipidus may suck vigorously during feeding but vomit immediately afterward (Saborio et al, 2000). Urine output is high, in excess of 5 ml/kg/hr, with low specific gravity (<1.010). Irritability and fever may accompany evidence of dehydration (poor skin turgor, depressed anterior fontanelle, sunken eyes, mottled skin, weak pulses, low blood pressure, and constipation).

Diagnosis. Serum electrolytes, osmolality, and plasma ADH levels are the primary laboratory tests used to diagnose DI. Plasma ADH is normally elevated in the newborn following delivery, playing a role in the low urine output that is typical on the first day of life. Hypernatremia as high as 180 mEq/L may be seen in DI, with elevated serum osmolality. Urinalysis reveals inappropriately dilute urine (low urine osmolality and low specific gravity). MRI is used to visualize the pituitary gland and stalk to delineate the cause of diabetes insipidus (Saborio et al, 2000).

Collaborative Management. Diabetes insipidus in neonates requires very careful fluid management. Severe dehydration and hypernatremia are corrected primarily with intravenous fluids (Muglia & Majzoub, 2004). Insensible water losses should be minimized. Serum electrolytes and osmolality,
blood glucose, accurate intake and output, and the evidence of dehydration (weight loss, blood pressure, pulses, skin turgor, etc.) should be closely monitored during treatment. Infants with severe hypernatremia must be observed for possible seizure activity. Although it is expected that serum sodium will decrease, very rapid shifts in serum sodium should be avoided. The infant’s neurologic status must be monitored closely for signs and symptoms of cerebral edema during therapy to correct serum sodium (Ferry, 2005). Hyperglycemia must be avoided as this may lead to glycosuria and exaggerate the diuresis. If it is not possible to manage DI with fluids alone, the agent of choice for pharmacologic treatment is desmopressin (DDAVP), a long-acting synthetic analogue of pituitary ADH. Intranasal DDAVP can be diluted with normal saline for administration to the neonate. Subcutaneous and oral formulations of DDAVP are also available, as well as short-acting intravenous aqueous pitressin for emergency treatment of severe dehydration. Caution must be observed when using vasopressin and high fluid intake to manage DI in the neonate because this combination can result in hyponatremia (Muglia & Majzoub, 2004).

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

SIADH is an impairment of free water clearance associated with inappropriately raised secretion of antidiuretic hormone (vasopressin). SIADH is believed to be associated with central nervous system infection and injury, such as birth asphyxia, intracranial hemorrhage, and meningitis.

Pathophysiology. An uncontrolled release of ADH can occur in sick preterm and term infants, resulting in renal free water retention that is inappropriate to the level of serum osmolality. The infant becomes hyponatremic, not because of true sodium depletion, but because of a dilutional effect from the fluid that is retained. ADH levels can become elevated in infants born after fetal distress, or those with severe pulmonary disease, undergoing surgery, or experiencing pain. Raised ADH levels are common in acutely ill neonates (Modi, 1998).

Clinical Manifestations. Signs and symptoms of SIADH are oliguria, hyponatremia, low serum osmolality (<275 mOsm/L), weight gain, and edema. Patients with SIADH are euovolemic or hypervolemic.

Diagnosis. The diagnosis of SIADH should be made when circulating ADH is elevated in the absence of both osmotic and baroreceptor stimuli (Modi, 1998). Serum electrolytes and osmolality reveal hyponatremia and hypo-osmolality. Urine reveals high sodium loss. There should also be normovolemia, normal blood pressure, and normal renal, cardiac, adrenal, and thyroid functions. True SIADH fulfilling all diagnostic criteria is probably uncommon in the neonate. Apparent SIADH may be due to hypovolemia-induced baroreceptor-driven ADH secretion, a normal response to reduced blood volume in the sick neonate (Modi, 1998).

Collaborative Management. Fluid restriction, with close monitoring of intake, output, serum electrolytes, blood glucose, accurate daily weights, evidence of increasing edema, and measures of hydration are the essentials of management. It can be difficult to restrict fluids because infants receive all of their nutrition in liquid form. Diuretics, such as furosemide, are sometimes used to promote free water excretion. Comparison of intake and output is important. A careful neurologic assessment should be performed, noting changes in relation to fluid or sodium balance.

THYROID GLAND

The thyroid gland is a butterfly-shaped structure made up of two lateral lobes connected by a thin band of tissue called the isthmus. Composed of densely packed follicular cells containing colloid, the thyroid gland also contains parafollicular cells (C-cells) that produce the calcium-lowering hormone calcitonin.

The thyroid hormones thyroxine (T4) and triiodothyronine (T3) are produced from the amino acid tyrosine. Essential to this process is the trapping and storage of iodide, a trace element required for thyroid hormone synthesis. Thyroglobulin (Tg), a thyroid hormone precursor, is synthesized in the follicular cell. Iodine is taken up by the Tg molecule, incorporated into its tyrosine residues, and returned to the colloid, where a coupling reaction takes place. This step, called organification, is catalyzed by the enzyme thyroid peroxidase (TPO). The coupling of two tyrosine residues produces T3, while the coupling of diiodotyrosine (DIT) with monoiodothy- roside (MIT) produces T4. These are stored in the follicular lumens until TSH stimulates their release into the circulation.

The thyroid gland produces mostly T4, which serves as a storage pool for T3. T3 is the most biologically active thyroid hormone, with greater affinity for the thyroid receptor. Circulating T4 is metabolized by outer-ring 5′ monodeiodination to T3 in the peripheral tissues. Inner ring 5′ monodeiodination of T4 produces reverse T3 (R3T3), an inactive metabolite. T4 and T3 circulate in plasma bound to thyroid-binding globulin (TBG), leaving just a small fraction in equilibrium as free hormone. It is possible for TBG, which is synthesized in the liver, to be deficient even though the free hormone levels are normal. It is the free hormone that is available to the tissues, with the bound hormone acting as a circulating reservoir. The concentration of free hormone determines the individual’s metabolic state.

The hypothalamic-pituitary-thyroid (HPT) axis controls thyroid hormone secretion (Figure 7-1). The hypothalamus synthesizes thyrotropin, stimulating release of TSH from the anterior pituitary. In turn, TSH stimulates uptake of iodine by the thyroid, thyroid hormone synthesis and release, and increased size and vascularity of the thyroid gland itself. The feedback loop is responsive to changes in free hormone concentration, and TSH secretion adjusts accordingly.

Fetal and Neonatal Thyroid Development

The thyroid gland is the first endocrine organ to develop in the human embryo (Park & Chatterjee, 2005). Concurrent with development of the fetal thyroid are growth and maturation of the hypothalamus and pituitary glands. At about 10 to 12 weeks’ gestation, the hypothalamus begins synthesizing TRH, the pituitary gland begins secreting TSH, and TBG is detectable in fetal serum. Maternal thyroxine is measurable in amniotic fluid before the onset of fetal thyroid function. Before 20 weeks’ gestation, this transplacental passage of maternal T4 largely provides for fetal thyroidal needs. By the start of the second trimester, however, the fetal contribution to circulating thyroid hormones is significant. The capacity of the fetal thyroid gland to trap and store iodide and synthesize thyroid hormones begins at about 11 weeks of gestation, but hormone production is limited until 18 to 20 weeks, when iodine uptake
translated TSH surge provokes rises in serum T4, T3, and free T4 to 100 munits/ml at 30 minutes after birth. This cold-stimulus, the pituitary releases a surge of TSH that peaks at 70 the newborn. In response to sudden exposure to a cold envi-

dinase. In the event of T4 deficiency, as in fetal hypo-

to T3 to provide a critical source of intracellular T3 to the

excess fetal T4 to the bio-inactive reverse T3 by type III deio-

2004). This is accomplished by preferential conversion of

generation of heat. An excess of bioactive T3 could be harmful

nervous system maturation but not for metabolism, growth, or

independently of maternal influence (Polk & Fisher, 2004).

Maternal hypothyroidism during early gestation can lead to

central nervous system damage in the fetus. Because the

placenta is impermeable to TSH, the fetal HPT axis develops

transplacental passage from the maternal circulation and

increases markedly. The only source of iodide for the fetus is

placenta. As pregnancy progresses, the placenta becomes less perme-
able to maternal thyroid hormone. Permeability is likely to be

highest during the first trimester because thyroid hormone is critical to fetal neurodevelopment, and there is no other source available to the fetus during this period. As the fetal HPT system matures, there is less dependence on maternally derived thyroid hormone for normal neurologic development. Maternal hypothyroidism during early gestation can lead to central nervous system damage in the fetus. Because the placenta is impermeable to TSH, the fetal HPT axis develops independently of maternal influence (Polk & Fisher, 2004).

During fetal life thyroid hormone is required for central nervous system maturation but not for metabolism, growth, or generation of heat. An excess of bioactive T3 could be harmful to fetal development. For this reason, the concentration of T3 is tightly controlled in the tissues (van Wassenaer & Koe, 2004). This is accomplished by preferential conversion of excess fetal T3 to the bio-inactive reverse T3 by type III deiodinase. In the event of T4 deficiency, as in fetal hypo-
thyroidism, T4 is shunted to the brain where it is deiodinated to T3 to provide a critical source of intracellular T3 to the developing brain.

Birth represents a temporary state of hyperthyroidism for the newborn. In response to sudden exposure to a cold envi-

ment, the pituitary releases a surge of TSH that peaks at 70

to 100 munits/ml at 30 minutes after birth. This cold-stimu-
lated TSH surge provokes rises in serum T4, T3, and free T4 that peak at about 48 hours. T4 increases in the majority of infants to 6.5 mcg/dl or more. The rise in T4 causes the TSH to decline to 20 munits/ml or less (the cutoff used in most screening programs for congenital hypothyroidism) because of feedback inhibition. Free and total T4 and T3 gradually decrease over the next 1 to 2 months.

**Congenital Hypothyroidism (CH)**

Congenital hypothyroidism is a deficiency of thyroid function present at the time of birth. With an incidence of 1 in 3000 to 4000 births, it is the most common congenital endocrine disorder. Early diagnosis and treatment are essential to prevent permanent neurologic damage. Because the majority of affected infants are asymptomatic at birth, neonatal screening for hypothyroidism is now mandated so infants with CH are promptly identified and treated. Most of the genetic mutations that produce CH can be sorted into two groups: those that cause thyroid dysgenesis and those that lead to dyshormonogenesis (Park & Chatterjee, 2005).

**Thyroid Dysgenesis**

The most common cause (85%) of permanent CH is thyroid dysgenesis, which includes thyroidal ectopy, hypoplasia, and complete thyroid agenesis. The severity of thyroid dysfunction is variable, depending on the amount of functional thyroid tissue that remains. Ectopic thyroid tissue (lingual, sublingual, subhyoid) may provide adequate amounts of thyroid hormone in some infants. Occasionally, ectopia are associated with thyroglossal duct cysts. A majority of these infants have a thyroid remnant, usually found midline at the base of the tongue, as a result of failure of the gland to descend normally during embryologic development.

Thyroid dysgenesis occurs in 1 in 4000 live births; however, the incidence in black infants is 1 in 32,000 live births and in Hispanic infants, 1 in 2000. The disorder has a female:male ratio of 2:1. Only 2% of thyroid dysgenesis is due to mutations in the homeobox genes that control thyroid differentiation (TTF-1, TTF-2, or PAX-8). Down syndrome is associated with an increased prevalence of thyroid dysgenesis. No serum Tg is measurable in thyroid agenesis, distinguishing it from functional thyroid tissue, which is associated with measurable serum Tg concentrations.

**Thyroid Dyshormonogenesis**

About 10% of infants with congenital hypothyroidism have inborn defects of thyroid hormone metabolism. Mutations in genes coding for proteins involved in thyroid hormone synthesis result in failure of one of the steps in this process, leading to thyroid insufficiency. These biochemical defects are usually inherited as autosomal recessive traits and include TSH hormone resistance, iodide organification defects, iodide transport defects, iodotyrosine deiodinase defects, and thyroglobulin deficiency. Deficient activity of the enzyme thyroid peroxidase (TPO) is one of the most common disorders of thyroid synthesis. Although dyshormonogenesis usually results in a compensatory goiter, it is not usually apparent during the neonatal period.

**Thyroid-Binding Globulin Deficiency**

Infants born with congenital TBG deficiency have low TBG and total T4 but normal TSH concentrations and are normal with respect to thyroid function. Familial congenital TBG deficiency, transmitted as an X-linked trait, occurs in 1 in 5000 newborns. The defect can be complete or partial and is usually an incidental finding on neonatal screening. A TBG level can be measured to confirm the diagnosis for the purpose of parental counseling, but no treat-ment is required.
Hypothalamic-Pituitary Hypothyroidism

Five to ten percent of infants with congenital hypothyroidism can be accounted for by what is called secondary-tertiary or central hypothyroidism. A deficiency of hypothalamic TRH or pituitary TSH can occur as a consequence of a developmental defect of the pituitary or hypothalamus. Central hypothyroidism is usually associated with other anomalies of the midbrain such as absence of the septum pellucidum or other midline defects, hypopituitarism, pituitary stalk interruption, or empty sella syndrome which lead to typical laboratory findings of low serum T₄, and low or inappropriately normal serum TSH.

Thyroid Hormone Resistance

An increasing number of patients are being found with resistance to the actions of endogenous and exogenous T₄ and triiodothyronine (T₃). Most patients have goiter, and levels of TSH in response to low T₃ and T₄ levels. Infants with suspect hypothyroidism in the neonate reflect the wide-ranging clinical manifestations of congenital hypothyroidism, including those born at home, those who are extremely ill in the neonatal period, and those who are transferred between states and throughout Canada.

Diagnosis of Congenital Hypothyroidism

Neonatal Screening. Routine screening of all newborn infants for congenital hypothyroidism has greatly improved early detection and treatment of the disorder, preventing much of the mental retardation that was previously associated with CH. The incidence of congenital hypothyroidism, as detected through newborn screening, is approximately 1 per 3000 to 4000. Screening all newborns for CH is mandated in all U.S. states and throughout Canada.

Most screening programs in North America initially measure T₄ on all specimens, measuring TSH only if T₄ is low. Owing to the physiologic surge in TSH in the first hours of life as the newborn adapts to the extrauterine environment, the screening specimen must be collected when the infant is at least 24 hours of age. If blood is collected earlier, particularly in the first 3 hours of life, a false positive result can occur. In those instances, a repeat specimen must be collected within the first 7 days of life, regardless of prior test results. Protein intake is not required prior to screening for CH.

False negatives can occur with screening; as many as 5% to 8% of infants with central CH can be missed with primary T₄ testing because their initial T₄ levels are in the normal range (Polk & Fisher, 2004). A similar problem can occur with infants who have hypothyroxinemia with delayed TSH elevation and those with residual thyroid tissue, such as an ectopic thyroid gland, because their initial T₄ levels are also in the normal range. All of these infants would be detected by repeat screening at 2 to 6 weeks of age.

Certain infants are at risk for a missed or delayed diagnosis, including those born at home, those who are extremely ill in the neonatal period, and those who are transferred between hospitals at an early age. Screening errors, including incorrect specimen collection, or improper storage and transport can lead to false negative results. Thyroid medications taken by the mother during pregnancy can also produce false negative results. Blood transfusions can alter test results. Preservatives (EDTA or citrate) in blood-collection containers can result in false negative or false positive screening results.

When a low T₃ and elevated TSH level (>40 munits/L) are encountered, the neonate should be presumed to have primary hypothyroidism until proven otherwise. A thorough examination for signs and symptoms of CH is indicated, along with confirmatory serum testing. Treatment with L-thyroxine should be initiated while awaiting the results of further testing.

Laboratory Testing. Low serum total and free T₄ and T₃, along with elevated TSH levels, confirm CH in the neonate. Permanent congenital CH is highly likely in a full-term neonate with a serum T₄ less than 6 mcg/dl and a serum TSH greater than 50 munits/L. A normal T₄ (e.g., >10 mcg/dl) in combination with elevated TSH suggests that the infant has enough functional thyroid tissue to respond to excess TSH stimulation, the pattern seen in a subgroup of infants with compensated or subclinical hypothyroidism. Age-related reference norms, for both gestational age and hours of age, should be used when interpreting all thyroid test results. If maternal antibody-mediated hypothyroidism is suspected,
maternal antithyroid (TSH receptor blocking, TRBAb) antibody testing should be done. Other thyroid autoantibodies that can produce hypothyroidism include thyroglobulin (TGA) and thyroperoxidase antibodies (TPOAb). Thyroid-binding globulin levels can be measured to rule out TBG deficiency. Thyroglobulin levels in infants with possible CH can help to differentiate between thyroid agenesis and dyshormonogenesis, as an adjunct to thyroid imaging.

**Imaging Studies.** Infants with biochemical evidence of CH usually undergo radionuclide scanning studies using iodine-123. Uptake of radioisotopes aids in detection of an ectopic (lingual or sublingual) or missing gland. A normal or enlarged gland on radioisotope scan suggests a defect in thyroxine synthesis as the source of CH. Thyroid ultrasound can also be useful initially to demonstrate presence or absence of a gland. Lateral radiographs of the knee and foot reveal bone age, indicating the degree of intratuerine hypothyroidism experienced by the fetus. Ossification of the distal femoral epiphysis usually appears at 36 weeks’ gestation; its absence in a term or post-term infant suggests delayed bone maturation from long-standing hypothyroidism.

**Collaborative Management of Hypothyroidism**

Early, adequate treatment of permanent CH is critical for optimal neurologic development. The goal of hormone replacement therapy is to rapidly normalize the infant's serum T4 level, and maintain it in the upper half of the normal range (Polk & Fisher, 2004). The agent of choice is sodium-L-thyroxine (NaT4) because it is substantially converted to T3 within the brain. Infants receiving thyroid replacement therapy must be monitored closely for adequacy of treatment and evidence of thyrotoxicosis (irritability, tachycardia, poor weight gain). Serum T4 should normalize in 1 to 2 weeks; serum TSH can take longer to normalize.

**Transient Disorders of Thyroid Function**

**Transient Hypothyroxinemia of Prematurity**

Preterm infants have the same incidence of permanent congenital hypothyroidism as full-term infants. In addition, about 50% of infants born at less than 30 weeks’ gestation exhibit transiently low thyroxine levels when compared to their full-term counterparts. This relative hypothyroxinemia is primarily a function of HPT axis immaturity, a physiologically normal stage of thyroid system development. However, many other factors influence thyroid function, particularly in the extremely preterm infant. The abrupt cessation of maternal T4 supply, occurring at the time of birth when demand for thyroid hormone is high, contributes to low thyroid hormone levels. Other factors include immature ability to concentrate iodine and to synthesize and iodinate thyroglobulin. Preterm infants may also suffer from insufficient iodine intake during the early weeks after birth before full enteral feeding is established. In addition, iodine excess related to the use of iodine-containing antiseptics and radiopaque agents can interfere with thyroid function by blocking thyroid hormone release from the thyroid gland.

**Pathophysiology.** The postnatal TSH surge of the preterm infant is similar, yet quantitatively lower, than that of the more mature infant. Likewise, the corresponding rise in T4 that occurs in preterm infants is blunted in comparison to term infants. It takes approximately 4 to 8 weeks, depending on the gestational age at birth, for normal term hormone levels to be reached (Polk & Fisher, 2004). The more severe the hypothyroxinemia, the more preterm the infant is. Infants with transiently low thyroxine need follow-up testing to ensure that the low T4 levels rise into the normal range over time.

Extremely preterm infants (24 to 27 weeks’ gestation) are at an even greater disadvantage, having a distinct and more ineffective pattern of postnatal thyroid function (Murphy et al, 2004). In these very immature infants, the TSH surge is significantly reduced, and TSH levels continue to fall after birth to less than cord blood values by 7 hours of age. Such very low TSH levels fail to stimulate a postnatal rise in T4 at all. T4 levels in extremely immature infants remain quite low after birth and are even slightly lower than cord blood values at 24 hours of age.

**Clinical Manifestations.** Hypothyroxinemia of prematurity is a subtle condition; there are no overt signs and symptoms of hypothyroidism. Many classic signs and symptoms of hypothyroidism are common clinical findings in the preterm infant (slow intestinal motility, distention, prolonged jaundice, low muscle tone, mottled skin, etc.).

**Diagnosis.** Hypothyroxinemia of prematurity is identified by routine newborn screening. T4 and free T4 are low, but TSH is not elevated above the cutoff of 20 munits/L. This is the critical difference between transient hypothyroxinemia of prematurity and congenital hypothyroidism. A repeat test is conducted after several weeks to recheck T4 and monitor for a possible delayed rise in TSH.

**Collaborative Management.** Although hypothyroxinemia of prematurity is associated with higher mortality and neurodevelopmental deficits, cumulative evidence to date has not been able to demonstrate clear benefits of routinely supplementing these infants with thyroxine during early infancy (van Wassenaar & Kok, 2004). The exception is the infant with an elevated TSH level; these infants require treatment. Thyroid function tests should be followed carefully in preterm infants at risk for hypothyroxinemia, and treatment should be instituted promptly when indicated. It is a good idea to flag or highlight the low thyroid results from the initial newborn screen to ensure that repeat thyroid testing is not overlooked.

**Nonthyroidal Illness**

In some ill preterm infants, T4 is preferentially converted to rT3 instead of T3, possibly as an adaptive response to lower the metabolic rate during times of severe illness (Ogilvy-Stuart, 2002). The outcome is low serum concentrations of both T4 and T3. Reverse T3 is elevated and TSH is normal. This condition, also known as low T3 syndrome or euthyroid sick syndrome, occurs in infants who have immature lungs or infections, because the cytokines produced in response to illness or inflammation are believed to inhibit thyroid function, metabolism, or thyroid hormone action (van Wassenaar & Kok, 2004). The low T3 from nonthyroidal illness reverses spontaneously when the infant’s condition improves, and no treatment is required. Similar effects are also seen in infants who are receiving dopamine or glucocorticoids, both of which can lower serum T4 concentrations.

**Transient Primary Hypothyroidism**

Hypothyroidism is defined as transient when a low T4 and elevated TSH in apparently healthy full-term infants revert to normal spontaneously or after several months of thyroxine supplementation. About 5% to 10% of the infants identified
by newborn screening programs as having congenital hypothyroidism eventually are recognized as having a transient condition. Initial management is the same as for CH.

Transplacental Passage of Drugs or Antibodies
One cause of transient hypothyroidism in the newborn is transplacental passage of antithyroid agents taken during pregnancy for the treatment of maternal Graves’ disease. Medications such as propylthiouracil (PTU), methimazole, radiiodine, and amiodarone can inhibit fetal thyroid production. A similar inhibitory effect can occur if the fetus is exposed to excess iodine in utero. If the mother has a history of autoimmune thyroid disease, maternal TSH receptor-blocking antibodies (TRBAb, also termed thyrotropin binding inhibitor immunoglobulin, or TBI) readily cross the placenta and block the fetal thyroid, producing hypothyroidism. These TRBAs can persist in the infant’s circulation for 2 to 3 months after birth before they are completely metabolized and disappear. However, it can be difficult to predict the effects of these antibodies because some mothers will simultaneously produce TSH-receptor stimulating antibodies that will offset the effects of the TRBAs.

Clinical Manifestations. Like congenital hypothyroidism, transient hypothyroidism is usually asymptomatic in the newborn. If present, the signs and symptoms are the same as for congenital hypothyroidism. Transient hypothyroidism caused by antithyroid drugs (goitrogens) can cause a goiter in the neonate. Iodine deficiency or excess has a similar effect.

Diagnosis. Transient hypothyroidism is usually detected by routine neonatal screening, or based on maternal history. The neonate displays the thyroid profile of low T4 and elevated TSH that is characteristic of hypothyroidism. When the maternal history is positive for autoimmune thyroid disease, TRBAb and TRSAb levels (as indicated) are also obtained for baseline purposes. Thyroid imaging tests may also be conducted.

Collaborative Management. Transient hypothyroidism caused by maternal antithyroid medication will resolve spontaneously when the medication is cleared from the infant’s circulation, usually within a day or two after birth. The infant’s serum T4 and TSH should be monitored to ensure that they return to normal. Supplementation with l-thyroxine is not usually necessary. Transplacentally acquired TSH receptor-blocking antibodies can be slow to degrade completely; therefore most infants will require supplementation for several months. TRBAb levels in the infant can be monitored to determine when to discontinue therapy. Breastfeeding is not contraindicated in neonates whose mothers who continue their antithyroid medication in the postpartum period, as very little transfers into the breast milk (Polk & Fisher, 2004).

Hyperthyroidism (Neonatal Graves’ Disease)
Pathophysiology. The transient condition neonatal Graves’ disease occurs in infants born to mothers with active or inactive Graves’ disease, or to those who have undergone thyroidectomy or radioiodine ablation of the thyroid gland. Maternal TSH-receptor stimulating antibodies (TRSAb or TSA) cross the placenta readily and stimulate the fetal thyroid gland, causing an overproduction of thyroid hormone and in some cases development of a goiter. Usually the higher the TRSAb level in the mother, the more severely affected the infant.

Hyperthyroidism in the neonate is usually transient, lasting approximately 3 to 12 weeks. The clinical course varies depending on characteristics of the mother’s disease and treatment. The onset of hyperthyroidism may be delayed for a week or longer in neonates whose mothers produce not only TRSAb but TSH receptor-blocking antibodies as well. Similarly, if the mother took antithyroid medication during pregnancy, the neonate might not exhibit evidence of hyperthyroidism for several days until the drugs are metabolized (and, in fact, may be hypothyroid during that time). Occasionally, the hyperthyroidism persists beyond the expected recovery period and becomes true, permanent Graves’ disease.

Clinical Manifestations. Neonates may be born preterm with evidence of intrauterine growth restriction. Common clinical signs of thyrotoxicosis include tachycardia, arrhythmias, hypertension, tachypnea, poor feeding, vomiting, sweating, hyperthermia, flushing, diarrhea, restlessness, tremors, irritability, and hyperalertness. In severe cases of untreated maternal Graves’ disease, advanced bone age, craniosynostosis, and microcephaly may be evident in both the fetus and newborn. The infant should be examined for a goiter, which can be very small or large enough to compress the trachea and cause respiratory distress in the newborn. A goiter is a symmetrical, smooth enlargement of the gland and can be recognized as a swelling in the anterior neck of the neonate (Figure 7-2). It is important to appreciate that a goiter can increase in size during the early neonatal period.

Diagnosis. Serum T4, free T4, and T3 are elevated, and serum TSH is low, all relative to age-appropriate norms. A TRSAb titer in the neonate will give an indication of the severity of the expected course of the disease. Infants at risk (e.g., high maternal titer of TRSAb) for severe thyrotoxicosis require frequent monitoring of free T4 and TSH. A good maternal history is essential (e.g., history of radioiodination therapy, antithyroid drugs taken during pregnancy and when they were taken, and maternal symptoms, if any).

Collaborative Management. The mainstays of treatment of hyperthyroidism in the neonate are iodine, antithyroid medication, sedation, and β-adrenergic blockers, if needed. Treatment is tailored to the severity of the infant’s symptoms. Lugol’s iodine solution (potassium iodide), given in

FIGURE 7-2
Newborn infant presenting at birth with goiter.
a single drop three times daily, acutely inhibits the release of thyroxine from the thyroid gland. Other preparations include iodine-based contrast agents (ipodate), PTU, and methimazole. Propranolol can be used to manage cardiovascular symptoms. The infant’s serum T3 must be followed closely during treatment to monitor for possible iatrogenic hypothyroidism. TRSAb levels are also followed to monitor the infant’s recovery and aid in determining the appropriate time for weaning antithyroid medication.

**ADRENAL GLAND**

The highly vascular adrenal glands are located at the superior poles of the kidneys. Each gland is composed of two distinct, independently functioning organs: the outer cortex, which produces steroid hormones (mineralocorticoids, glucocorticoids, and androgens), and the inner medulla, which produces catecholamines. Adrenal steroid production and regulation require a functional hypothalamic-pituitary-adrenal (HPA) axis. Cortisol is also released in response to stress, hypoglycemia, surgery, extreme heat or cold, hypoxia, infection, or injury. Adrenal androgens include dehydroepiandrosterone (DHEA), DHEA sulfate, and androstenedione and are regulated by ACTH. These steroids have minimal androgenic activity but are converted in the peripheral tissues to two more potent androgens, testosterone and dihydrotestosterone (DHT).

**Fetal Adrenal Gland**

The fetal adrenal is evident from 6 to 8 weeks of gestation and rapidly increases in size. Early in gestation, the fetal adrenal cortex differentiates into three regions: an inner prominent fetal zone, an outer definitive zone, and a transitional zone. After birth, the fetal zone involutes and the definitive zone forms the mature gland. Cortisol maintains intrauterine homeostasis and influences the development of a wide variety of fetal tissues. Cortisol is essential for prenatal maturation of organ systems including lungs, GI tract, liver, and the CNS which are vital for neonatal survival.

The fetal adrenal gland and the placenta are an integrated endocrine system known as the fetoplacental unit. The fetal zone of the developing adrenal gland produces DHEA and DHEA sulfate, precursors for placental estrogen, which is critical to maintenance of the pregnancy and fetal well-being. In turn, the placenta regulates fetal sodium and water retention and potassium excretion. Aldosterone affects not only electrolyte balance but blood pressure and intravascular volume as well. Aldosterone is regulated by the plasma renin-angiotensin system, which in turn stimulates production of aldosterone.

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**Neonatal Adrenocortical Function**

Plasma cortisol levels are elevated at the time of birth but decline in the first few days of life. In term infants, a nadir is seen on day 4 of life. Likewise, levels of cortisol precursors such as 17-hydroxyprogesterone (17-OHP) are high at birth but decrease to normal neonatal levels by 12 to 24 hours of age. Cortisol is regulated by pituitary ACTH, which in turn is controlled by hypothalamic CRH via a negative feedback loop. Aldosterone and plasma renin activity are elevated in neonates compared with values for older infants, allowing for positive sodium balance until the kidneys fully mature. The hyponatremia and urinary sodium losses often seen in preterm infants during the early postnatal weeks are due to a relative mineralocorticoid deficiency as a consequence of immaturity of both the kidneys and the adrenal glands.

**Adrenal Disorders in the Neonate**

**Transient Adrenocortical Insufficiency of Prematurity**

A limited ability of the adrenal glands to maintain cortisol homeostasis in the early days of life has been observed in some preterm newborns. Manifestations are a low serum cortisol, normal or exaggerated pituitary response, and good recovery of adrenal function by day 14 of life. A proportion of very low birth weight infants with inotrope and volume-resistant hypertension show an inadequate adrenal response to stress in the immediate postnatal period (Ng et al, 2004).

**Adrenal Hemorrhage**

Adrenal hemorrhage in the neonate can occur as a result of traumatic delivery, breech presentation, macrosomia, or defective coagulation. The large size and vascularity of the fetal adrenal gland may predispose it to injury and rupture during the birth process. Classic findings include a flank mass on either side, with discoloration and purpura of the overlying skin. In severe cases, the infant may exhibit signs of adrenal insufficiency and anemia.

**Congenital Adrenal Hyperplasia**

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from a deficiency of one of the five enzymes required to synthesize cortisol from cholesterol in the adrenal cortex. Each enzyme is encoded by its own gene, and mutations in the 21-hydroxylase gene, CYP21, are the most frequent. 21-Hydroxylase (21-OHD) deficiency accounts for 95% of CAH and is the most common cause of ambiguous genitalia of the neonate.

**Pathophysiology.** A lack of 21-hydroxylase prevents conversion of progesterone to its two end products: cortisol and aldosterone (Figure 7-3). By reduced negative feedback regulation, the absence of cortisol causes oversecretion of ACTH, which chronically stimulates the adrenal cortex, resulting in hyperplasia of the gland. The precursor steroids proximal to the blocked step accumulate and are shunted into other metabolic pathways such as androgen biosynthesis. In a female fetus, these superfluous yet potent systemic androgens cause virilization of the developing external genitalia. Also important may be the effects of this androgen exposure on the developing central nervous system (Berenbaum, 2004). Internal reproductive organs (ovaries, fallopian tubes, and uterus) are not affected by androgen exposure and develop normally.

Classic 21-OHD has a worldwide incidence of about 1 in 15,000 live births (Therrell, 2001). Two-thirds of those have a severe form known as salt-wasting or salt-losing in which there is a concurrent inability to produce aldosterone. High sodium excretion leads to profound hyponatremia, dehydration, and hyperkalemia. Glucocorticoid deficiency impairs carbohydrate
metabolism, resulting in hypoglycemia and leading to hypo-
tension, shock, and cardiovascular collapse from adrenal insuf-
ficiency. The remaining one-third has a simple virilizing form.
These infants have an incomplete enzymatic block, with
enough aldosterone biosynthesis to maintain fluid and
electrolyte homeostasis.

Clinical Manifestations. Affected female infants are
usually recognized at birth by their nontypical genitals. A
range of findings is possible, including clitoromegaly, posterior
fusion of the labia majora, and a single perineal orifice instead
of separate urethral and vaginal openings (Merke & Bornstein,
2005). In the last instance, the vagina joins the urethra above
the perineum, forming a single urogenital sinus. In severe cases,
clitoral hypertrophy is so marked that it resembles a penile
urethra (Figure 7-4). These infants can be mistaken for boys
with bilateral cryptorchidism and hypospadias. There may also
be hyperpigmentation of the genital skin resulting from exces-
sive pituitary ACTH secretion. Male infants with 21-OHD are
phenotypically normal and may not be identified in the imme-
 diate neonatal period, because the onset of adrenal symptoms
is delayed until 7 to 14 days of life. Undetected infants may
present to the emergency room with signs and symptoms of
impending adrenal collapse: vomiting, weight loss, lethargy,
dehydration, hypotension, hyperkalemia, hypoglycemia,
hypovolemia, and shock.

Diagnosis. A markedly elevated 17-hydroxyprogesterone
(17-OHP) level is diagnostic for classic 21-hydroxylase defi-
ciency. Random 17-OHP levels in affected infants can reach
10,000 ng/dl (normal is <100 ng/dl) (Speiser & White, 2003).
However, such high 17-OHP levels may not be reached until
the second or third day of life, so a specimen drawn too early
could lead to false reassurance that the infant does not have
CAH. Biochemical support for the diagnosis of CAH also includes elevated serum DHEA and androstenedione levels in males and females, and elevated serum testosterone in females. Molecular genetic analysis is not usually essential for the diagnosis but may be helpful to confirm the exact type of defect and to aid in genetic counseling.

Part of the evaluation of every newborn with ambiguous genitalia is a karyotype or FISH test for sex chromosome material, and this is also true when the suspected diagnosis is CAH. Some infants are so externally virilized that it might be difficult for parents to believe the infant is genetically female without the proof presented by chromosome testing. Imaging studies, including pelvic and abdominal ultrasound, will determine the presence or absence of a uterus, evaluate adrenal size, and more rapidly identify the gender of the infant.

The increased serum 17-OHP levels in affected infants permit screening for the disorder using blood filter specimens on routine newborn screening panels. The major objectives of newborn screening for CAH are the presumptiv identification of infants at risk for the development of life-threatening adrenal crises and prevention of incorrect sex assignment of affected female infants with ambiguous genitalia. The former is particularly important for affected boys whose initial manifestation may be adrenal crisis. Currently 42 of 50 states either have programs already in place or have mandates for screening newborns for congenital adrenal hyperplasia (NNSGRC, 2005). False positives can occur in preterm infants or sick infants, both of whom have higher levels of 17-OHP.

**Collaborative Management.** The newborn with CAH requires urgent expert medical attention. When the diagnosis of CAH is confirmed, physiologic replacement dosage of cortisol is begun in order to suppress ACTH and androgen overproduction, but not enough to completely suppress the HPA axis (Merke & Bornstein, 2005). Aldosterone replacement maintains fluid and electrolyte homeostasis. Agents of choice in the newborn are hydrocortisone, a glucocorticoid, plus fludrocortisone, a mineralocorticoid. Further clinical management is guided by daily weights, adrenal steroid concentrations, plasma renin activity (PRA), electrolytes, blood glucose, and other data. Plasma renin activity should be compared to age-specific norms, because basal PRA is higher in the newborn than in older infants. Dietary sodium chloride supplementation is often necessary.

The overwhelming majority of 46XX individuals with CAH develop a female gender identity, regardless of the degree of genital virilization present at birth, according to currently available evidence (Berenbaum, 2004). Therefore, even in cases where babies are initially “misassigned” as boys, it is still generally recommended that these genetic females with CAH be raised as females (Berenbaum, 2004; Brown & Warne, 2005). Hypertrophy of the clitoris will gradually abate with androgen withdrawal. The clitoris will regress at 11 weeks’ gestation. Müllerian ducts require no hormonal stimulation to regress. By the 9th week, testicular Leydig cells are secreting androgenic hormones.

The next events in sexual development are hormonally mediated. By 7 weeks of gestation, the fetus has two sets of primitive ducts that will become the internal reproductive tracts: the müllerian (female) and wolffian (male). In the XY fetus, the testis differentiates by the end of week 7. The embryonic testis develops two types of hormone-producing cells: the Sertoli and the Leydig cells. The Sertoli cells begin secreting müllerian-inhibiting factor (MIF), causing the müllerian ducts to regress. By the 9th week, testicular Leydig cells are secreting androgens necessary for further virilization of the male fetus.

Testosterone, the major androgen produced by the testes, acts locally in high concentrations to induce development of the wolffian ducts into the epididymis, vas deferens, and seminal vesicles. In the absence of testosterone, the wolffian ducts regress at 11 weeks’ gestation. Müllerian ducts require no ovarian hormonal inducement to develop into Fallopian tubes, uterus, and upper vagina. This occurs in fetuses with a normal ovary or on any side lacking a gonad.

**External Genitalia**

The primitive external genital structures are identical in both sexes (Figure 7-5). In this indifferent stage, a genital tubercle forms and elongates to form a phallus and urogenital sinus, surrounded by inner urogenital folds and labioscrotal swellings. Between the 8th and 14th weeks of gestation, male differentiation of the external genitalia takes place. Central to this development is availability of dihydrotestosterone (DHT), a potent metabolite produced from testosterone by the enzyme 5α-reductase-2. With 10 times the binding affinity of testosterone, DHT binds to androgen receptors in the genital tissues, stimulating fusion of the urethral folds to form the penile shaft, and the labioscrotal swellings to form the scrotum (Federman, 2004). The urogenital sinus becomes the urethra. Penile growth continues throughout gestation, and migration of the
testes from the abdominal cavity to the scrotum does not occur until 25 to 35 weeks’ gestation.

In the absence of DHT, feminization of the external genitalia occurs. The phallus becomes a clitoris, and the labio-scrotal swellings remain unfused to form the labia majora and minora. The urogenital sinus develops into the lower vagina and urethra. Feminine external genital development is complete by 11 weeks’ gestation. Androgen exposure after this critical period can promote growth of the clitoris but does not cause labial fusion or the development of a penile urethra (Houk & Lee, 2005).

Disorders of Sexual Development

A disorder of sexual development (DSD) is a congenital disorder with atypical development of chromosomal, gonadal, or anatomic sex (Lee et al, 2006). The majority of DSDs result from one of two conditions: either a failure in one of the steps of the male developmental pathway, or the exposure of an XX fetus to androgens during a sensitive period of development.

46XX DSD

The most frequently encountered intersex condition in the neonate is the virilized female, or the 46XX infant with ambiguous external genitalia but normal female internal structures (Forest et al, 2004). The most common etiology is congenital adrenal hyperplasia, caused by 21-hydroxylase deficiency (21-OHD). This enzyme deficiency results in an overproduction of androgens at a critical stage of development, causing masculinization of the external, but not the internal (ovaries, uterus, fallopian tubes), genitalia. In the most severe cases, the excess androgens also prevent the vagina from fully descending into the perineum, leaving a common urogenital canal. (See previous section, Adrenal Disorders.)

Other possible, yet rare, causes of virilization of external genitalia in the 46XX infant are placental aromatase deficiency, maternal androgen-producing or adrenal tumors, and maternal medications with androgenic action taken during pregnancy.

46XY DSD

The combination of a 46XY karyotype with ambiguous genitalia results from a failure in one of the steps involved in the synthesis or response to testosterone during sexual differentiation and penile growth. These infants have bilateral testicular development, but incomplete virilization of the internal or external genitalia. This results in an external phenotype ranging from completely female to isolated hypospadias or cryptorchidism. Another condition associated with incomplete virilization in the XY male is cloacal extrophy, a defect
of embryogenesis involving exstrophy of the bladder. Although not a DSD, significant ambiguity of external genitalia may be present.

**Androgen Insensitivity Syndrome (AIS)**

**Pathophysiology.** AIS is caused by a loss-of-function mutation in the androgen receptor gene located on the long arm of the X chromosome. Both testosterone and its target tissue metabolite, DHT, must bind to androgen receptors in order to masculinize the genital tissues. When androgen receptor activity is impaired, androgen binding is insufficient. One variant of AIS is receptor negative: cytosol receptors are incapable of binding DHT. Another variant is receptor positive: receptors are able to bind DHT but this does not result in normal differentiation. Both internal wolffian structures and external genitalia fail to respond to high levels of testosterone and DHT. There are partial and complete forms of the disorder, resulting in different degrees of undervirilization. In partial androgen insensitivity syndrome (PAIS) the clinical phenotype varies considerably and often parallels the severity of androgen resistance.

**Clinical Manifestations.** Infants with PAIS have undervirilization ranging from simple hypospadias to microphallus with a labia majora-like bifid scrotum, undescended testes, and a urogenital sinus. No visible features distinguish PAIS from other causes of incomplete masculinization. Infants with complete androgen insensitivity (CAIS) are born with apparently female genitalia. However, these neonates may have palpable inguinal or labial masses, which further testing will reveal to be testes. Some may also have a short, blind-ending vagina.

**Diagnosis.** The diagnosis of CAIS is missed in the newborn period unless the infant presents with bilateral masses in the labia or inguinal canals or a boy was expected based on a prenatal karyotype. CAIS might also be discovered at the time of inguinal hernia repair (Hyun & Kolon, 2004), or there may be a history of similarly affected family members. Important investigations include a karyotype, levels of testosterone, DHT, and LH, and genital skin fibroblasts for androgen-binding activity. Imaging studies reveal the absence of female internal reproductive structures (uterus, fallopian tubes). Two normal testes are present.

**Collaborative Management.** Infants with CAIS have unambiguously female external anatomy and are raised in the female gender. Testes are removed (usually after puberty) to prevent later malignancy. The gender assignment of infants with PAIS can be more complex and is often based on the severity of the phenotype (Misra & Lee, 2005). When the phenotype is predominantly male, a male sex of rearing is recommended. However, there are no consensus guidelines for the management of infants with severe perineoscrotal hypospadias and microphallus. The detection of somatic mutations in AIS is of importance for correct sex assignment because the presence of a functional wild-type AR receptor can induce virilization at puberty (Kohler et al, 2005). When a male sex of rearing is contemplated, a therapeutic trial with pharmacologic doses of androgen, especially in those with an identified AR mutation, is often used to predict potential androgen responsiveness at puberty. If there is no phallic growth in response to testosterone, some have recommended consideration of a female gender assignment. However, many experts now believe that, given the putative influence of prenatal androgen exposure on the developing central nervous system, and the possibility that the child will develop a male gender identity, it is more prudent to raise these infants as boys.

**Testosterone Biosynthetic Defects**

**Pathophysiology.** Defects in the chain of steroidogenic enzymes involved in the testosterone biosynthesis pathway result in insufficient androgen concentrations during fetal development. Disorders include congenital lipoid adrenal hyperplasia (CLAH), 3ß-HDD, 17ß-hydroxysteroid dehydrogenase deficiency (17ß-HSD). CLAH is caused by a defect in the steroidogenic acute regulatory (StAR) protein, responsible for transporting cholesterol to the inner membrane of the mitochondria. Insufficient testosterone in affected males leads to underdeveloped wolffian duct structures and external male anatomy. Mullerian structures are absent because there is normal testicular MIF production.

**Clinical Manifestations.** Male infants with CLAH present with complete adrenal insufficiency: vomiting, weight loss, and hypotension. Genital appearance is primarily female. Infants with 3ß-HDD can present with varying degrees of genital ambiguity and evidence of salt-losing crisis (see 21-OHD). Infants with 17ß-hydroxysteroid dehydrogenase deficiency have genital ambiguity; with primary 17ß-hydroxylase deficiency patients also have hypertension. These male infants with 17ß-HSD present with what appears to be external female genitalia that may include mild clitoral enlargement. An inguinal hernia may be present, possibly the only finding that will bring the infant to medical attention.

**Diagnosis.** General laboratory investigations in suspected testosterone biosynthetic defects include chromosomes, baseline levels of testosterone, androgen precursors and DHT, and levels of steroids and steroid precursors. An hCG stimulation test can be performed to measure the ratio of androstenedione to testosterone; an elevated ratio suggests 17ß-HSD deficiency.

**Collaborative Management.** Acute management of these disorders requires full steroid replacement with both glucocorticoids and mineralocorticoids. In CLAH and 3ß-HDD, general supportive measures may be necessary, as severe adrenal insufficiency can cause rapid metabolic decompensation if the disorder is not recognized at birth (Misra & Lee, 2005). Genetic XY infants with CLAH are raised in the female gender. Children with 17ß-HSD often virilize significantly at puberty owing to increased peripheral conversion of androstenedione to testosterone by 17ß-HSD isoenzymes, making gender assignment of those diagnosed as neonates a less straightforward decision.

**5α-Reductase-2 Deficiency (5-ARD-2)**

**Pathophysiology.** 5-ARD-2 deficiency is an autosomal recessive disorder caused by more than 20 different mutations of the 5-ARD gene. 5-ARD-2 is an enzyme found in the genital skin and fibroblasts of the developing fetus, without which testosterone is not converted to DHT, and fetal external genitalia do not virilize. Development of the internal structures is unaffected because DHT is not required, so the wolffian ducts differentiate normally in response to testosterone and the mullerian ducts regress. At puberty, the external genitalia become virilized and fertility is possible (Misra & Lee, 2005).
**Clinical Manifestations.** The spectrum of findings ranges from mild undervirilization (isolated micropenis or hypospadias) to severe undervirilization (a female phenotype with clitoromegaly, mild rugation, or pigmentation) (Figure 7-6). Testes are intact and are found in the inguinal canals or labioscrotal folds, or are retained in the abdomen. The uterus and fallopian tubes regress because of normal secretion of MIS. Wolffian duct differentiation is not affected because DHT is not required. Male internal ducts terminate either in a blind pseudovaginal pouch or on the perineum.

**Diagnosis.** Diagnosis is made by assessing the ratio of testosterone to DHT following an hCG stimulation test. A normal T/DHT ratio is less than 10:1. In 5-ARD-2 deficiency, this ratio is elevated. The hCG stimulation test also rules out other causes of undervirilization, such as Leydig cell hypoplasia and testosterone biosynthetic defects. Analysis of 5-ARD-2 activity in genital skin fibroblasts provides a definitive diagnosis.

**Collaborative Management.** Boys with 5-ARD-2 respond to endogenous testosterone and undergo virilization and penile growth at puberty. The mechanism behind this late virilization may be extraglandular DHT formation due to peripheral conversion of increased testicular testosterone by unaffected isoenzymes (Sultan et al, 2002). For this reason, it is recommended that when the diagnosis is made in the newborn period, a male sex assignment should be made (Goodwin & Caldamone, 2004).

**Gonadal Dysgenesis**

This group of disorders is usually associated with chromosomal anomalies or mutations or deletions of genes responsible for sexual differentiation. Karyotypes producing gonadal dysgenesis include 46XY, 46XX, 46XY/46X, and mosaic forms including the Y chromosome. Gonadal dysgenesis can occur as an isolated condition or as part of a complex syndrome such as Fraser, Denys-Drash, or campomelic dysplasia (Brown & Warne, 2005).

**Pathophysiology.** A dysgenetic testis either fails to produce testosterone at all or produces insufficient testosterone, resulting in varying degrees of undervirilization of the fetus. The most likely cause of gonadal dysgenesis is a mutation in the sex-determining gene (Palma Sisto, 2004). Gonadal dysgenesis is considered partial or incomplete when the testes are dysgenetic or incompletely formed, and complete when the gonads are streaks containing only stromal tissue. Mixed gonadal dysgenesis occurs when one gonad is a streak and the other is a well-formed testis. The internal ducts correlate with the ipsilateral gonad. On the side of a streak gonad, a fallopian tube and a hemiuterus will develop, and on the side of a normal testis, the vas deferens and epididymis will form.

**Clinical Manifestations.** The external genitalia are highly variable depending on how much testosterone is produced. In mixed gonadal dysgenesis, the external genitalia are asymmetric, appearing male on one side and female on the other. A vagina and uterine cavity may be present. Complete (or pure) gonadal dysgenesis is a form of sex reversal that results in unambiguously female genitalia with features of Turner’s syndrome. These infants might not be identified in the newborn period unless a discrepancy is noted between a prenatal karyotype (46XY) and appearance of the genitals.

**Diagnosis.** Determining the sex chromosome complement by FISH testing is the most important diagnostic test. Imaging studies, genitography, or laparoscopy is used to define the internal anatomy. Gonadal histologic analysis is necessary to differentiate gonadal dysgenesis from true gonadal intersex, a condition wherein elements of both testes and ovaries are present in the same individual (see later discussion).

**Collaborative Management.** Determining the sex of rearing for the infant with partial or mixed gonadal dysgenesis can be a difficult decision, one that is usually based on the degree of virilization and details of the internal anatomy (Goodwin & Caldamone, 2004). When a uterus is present, the female sex assignment may be preferred. Most infants with complete gonadal dysgenesis are raised as females.

**Ovotesticular DSD**

In ovotesticular DSDs both ovarian and testicular components are present in the same individual (Houk et al, 2005). Possible combinations include an ovary on one side and a testis on the other, an ovary or testis with an ovotestis, or two ovotestes. More than half of affected babies will have an XX karyotype. This condition was formerly known as true hermaphroditism, a label that is considered outdated.

**Pathophysiology.** The amount of testosterone produced by the testicular tissue that is present determines the degree of differentiation of wolffian ducts, regression of Müllerian ducts, and virilization of external genitalia. The internal ducts usually parallel the ipsilateral gonadal histology. Ovarian tissue can be normal.

**Clinical Manifestations.** Asymmetry of the external genitalia is common. Genital ambiguity ranges from a female phenotype with slight clitoromegaly to a mildly undervirilized male phenotype. The most common presentation is marked genital ambiguity: microphallus with penoscrotal or perineoscrotal hypospadias, fusion of labioscrotal folds, and cryptorchidism (Misra & Lee, 2005).
Diagnosis. FISH testing is used to determine sex chromosome complement. Imaging studies are used to define the internal anatomy. To diagnose true gonadal intersex, the presence of functional ovarian tissue containing follicles and testicular tissue with distinct seminiferous tubules must be established (Misra & Lee, 2005). Laparoscopy with gonadal biopsy is necessary at some point to confirm the diagnosis.

Collaborative Management. Principles of management for infants with true gonadal intersex are similar to those of gonadal dysgenesis.

General Principles of Management of DSDs

The fact that doctors and nurses are not quite sure if one’s long-awaited newborn baby is a boy or a girl must surely be one of the most incomprehensible things that parents can hear in the delivery room. This situation requires a high degree of sensitivity and tact. Many infants are identified prenatally following ultrasound recognition of genital ambiguity or a karyotype/phenotype discordance, and these families will be prepared, to some degree, for the experience of having a baby of uncertain sex. Others will be taken completely by surprise. In spite of the family’s desire for a quick answer, no attempt should be made by medical professionals at the time of birth to guess the sex of the baby (Ogilvy-Stuart & Brain, 2004). The extreme phenotypic heterogeneity seen in DSDs makes it impossible to accurately predict either the diagnosis or the karyotype from a brief genital examination (Houk & Lee, 2005).

The Lawson Wilkins Pediatric Society and the European Society for Paediatric Endocrinology recently established an International Consensus Conference on Intersex. The result was a consensus statement on management of intersex disorders (Lee et al, 2006). That document represents the first agreed-on set of guiding principles for approaching and managing the newborn with a DSD.

Clinical Manifestations. Essential to the evaluation of the neonate with genital ambiguity is obtaining a detailed family history. Any of the following might suggest a congenital or inherited DSD: maternal virilization or ingestion of hormones or oral contraceptives during pregnancy; consanguinity; history of urologic abnormalities, infertility, or genital ambiguity in other family members; or previous neonatal deaths that might suggest an undiagnosed adrenal crisis. Dysmorphic features suggest the possibility of a syndrome.

A detailed assessment of the genitalia should be conducted. This and all subsequent examinations should respect the privacy of the infant and the family as much as possible, avoiding overexposure of the infant even for educational purposes (Houk & Lee, 2005). Although the physical assessment alone does not permit a firm diagnosis, some assessment findings can guide the diagnostic process in one direction or another. A precise description of the anatomy is more useful than simple staging classifications. If preferred, however, the degree of virilization can be documented by Prader staging from a phenotypic female with mild clitoromegaly (Prader stage II) to phenotypic male with glandular hypospadias (Prader stage V) (Figure 7-7). Look for symmetry or asymmetry of the genitalia. The presence of a uterus can be determined by digital rectal examination as an anterior midline cordlike structure (Hyun & Kolon, 2004).

Gonads. Determine whether gonads are palpable. Presence or absence of palpable gonads helps to differentiate the major categories of DSDs. An apparent male infant with bilateral or a single impalpable testis with hypospadias should be regarded as having a potential DSD until proven otherwise. A palpable gonad excludes the diagnosis of virilized genetic female (46XX) with CAH. A gonad palpated below the external inguinal ring is presumed to contain testicular tissue. Because ovaries are rarely palpable, a unilateral gonad is usually a testis or occasionally an ovotestis. To palpate testes, place finger flat from internal ring, and milk down into the labioscrotal folds. Gonads may be situated high in the inguinal canal, requiring a careful examination. Sweep the fingers down along the line of the inguinal canal on each side, beginning well above the site of the internal inguinal ring. A gonad milked down by this maneuver is gently grasped by the other hand and its size and consistency noted. Ovotestes are softer and less homogenous than testes (Brown & Warne, 2005). Bilateral absence of the testes is known as cryptorchidism.

Phallus. Phallic size should be measured with a straight-edge ruler, depressing the fat pad and measuring the stretched length from pubic tubercle to tip of penis, not including the foreskin. Both length and diameter of the penis should be noted. Chordee (ventral curvature of the penis) should be evaluated.

Clinical staging is an important assessment tool (Figure 7-7). The Lawson Wilkins Pediatric Society and the European Society for Paediatric Endocrinology recently established an International Consensus Conference on Intersex (Lee et al, 2006). That document represents the first agreed-on set of guiding principles for approaching and managing the newborn with a DSD.

FIGURE 7-7
Degrees of genital virilization according to the stages of Prader. The upper panel shows sagittal view and the lower panel shows perineal view. From Sperling M, editor. Pediatric endocrinology, ed 2 (p 406). Philadelphia: Saunders.
be noted as it may decrease the apparent length of the penis. The actual position of the urethral meatus should be determined. Clitoral size should also be measured when clitoromegaly is present. Clitoral length greater than 9 mm in term infants is considered excessive. Clitoral size often appears large in preterm infants because breadth remains constant from 27 weeks onward. A prominent, but not truly enlarged, clitoris, or a normally sized penis concealed by an abundance of prepubic fat are two normal assessment findings that sometimes prompt referrals for genital ambiguity (Houk & Lee, 2005).

**Labioscrotal Folds.** Labial fullness, a benign finding, is another feature occasionally mistaken for genital ambiguity. The labioscrotal folds are examined for fusion, which starts posteriorly and moves anteriorly, increasing the anogenital distance. The perineum is inspected by gently separating the labia and using an exam light to confirm the presence of separate urethral and vaginal openings or a single urogenital orifice (an opening connected to both urinary and genital systems). If skin tags with slightly bluish hue are seen, a hymen and vagina are palpable. Note rugosity or hyperpigmentation of the labioscrotal fold, signifying hyposecretion of ACTH associated with CAH.

**Diagnostic Studies.** DSDs are diagnosed with a combination of biochemical, hormonal, and genetic testing. The principal aim of an initial investigation is to rule out a life-threatening illness such as congenital adrenal hyperplasia, which can precipitate an adrenal crisis. Such testing includes serum 17-hydroxyprogesterone (17-OHP) level (after 24 to 48 hours of age), electrolytes, glucose, baseline levels of testosterone, DHT, and other steroid precursors (progesterone, dehydroepiandrosterone, Δ^4-androstenedione, and 17α-hydroxyprogrenenolone). A karyotype with X- and Y-specific probe detection is obtained from all infants, even if a prenatal karyotype is available (Lee et al, 2006).

A urinary steroid profile is helpful in the diagnosis of disorders of steroid biosynthesis. Other investigations that may be warranted include ACTH stimulation test, plasma renin activity, and serum MIF, LH, and FSH. An hCG stimulation test is undertaken to delineate a block in testosterone biosynthesis from androstenedione (17β-hydroxysteroid dehydrogenase deficiency) or conversion of testosterone to DHT (5α-reductase deficiency). An hCG test involves measuring baseline levels of testosterone and its precursors DHEA or DHEA sulfate and androstenedione and its metabolite DHT. One to three intramuscular injections of high-dose hCG are given at 24-hour intervals, and repeat testosterone levels are drawn at 72 hours or 24 hours after the last injection (Ogilvy-Stuart & Brain, 2004).

Imaging studies include pelvic ultrasound to determine presence or absence of gonads in the inguinal region and to assess the müllerian anatomy, pelvic MRI, and urogenital sinusogram (retrograde injection of contrast into urogenital sinus opening to confirm presence of and delineate anatomy of lower vagina). Laparoscopic exploration with gonadal biopsy may be necessary to evaluate gonadal histology. Finally, molecular genetic analysis may be required to arrive at a definitive diagnosis for some disorders.

**Interpretation of Findings.** The most common cause of genital ambiguity in the newborn is 21-hydroxylase deficiency. This form of congenital adrenal hyperplasia, responsible for over 90% of cases of ambiguous genitalia, presents with a virilized XX (female) infant. Among the remainder of cases of ambiguous genitalia, the most common diagnoses are gonadal dysgenesis, followed by partial androgen insensitivity syndrome, and testosterone biosynthetic disorders (Brown & Warne, 2005). It is not always possible to reach a diagnosis in the undervirilized male infant. In a study of 67 XY infants with external sexual ambiguity, testicular tissue, and/or a XY karyotype, in 52% of cases, no diagnosis could be reached, despite an exhaustive clinical and laboratory workup, including sequencing of the androgen receptor (Morel et al, 2002). Provisional diagnostic groupings can be determined based on presence or absence of a uterus, symmetry of the external genitalia, and presence of gonads (Table 7-1), providing a basis for more focused additional investigations (Brown & Warne, 2005).

**Talking with Families.** Optimal care of the infant with a DSD involves a well-coordinated team approach. The team comprises at minimum the attending neonatologist, neonatal nurse, endocrinologist, pediatric surgeon/pediatric urologic surgeon, social worker, counselor or other mental health professional, and in some instances, geneticist. The initial contact with parents of a newborn with a DSD is extremely important. This interaction should emphasize that a DSD is not a shameful condition and does not preclude the child from becoming a well-adjusted, functional adult (Lee et al, 2006). A single person should be identified to communicate diagnostic findings and plans with the family. When discussing possible diagnoses with the family, language must be carefully chosen. The terms “hermaphrodite” and “pseudohermaphrodite” are outdated, confusing, and perceived as distasteful by many (Houk et al, 2005). These words should be avoided, and instead, accurate, informative terms that describe the infant’s diagnosis should be used. Clear explanation of sexual development in the fetus will help parents understand how an infant can be born with atypical genitalia, an important component of parental coping (Houk & Lee, 2005). It is the parents who have the responsibility to make or defer decisions about care for their infant with a DSD, including gender-of-rearing (Houk & Lee, 2005). The role of the health care team is to provide information, to share and explain all diagnostic findings, to inform parents of all available options, and to support the parents in the decision-making process. The approach should be family-centered as well as culturally sensitive (Thyen et al, 2005). Family concerns must be respected and addressed in strict confidence (Lee et al,

<table>
<thead>
<tr>
<th>TABLE 7-1</th>
<th>Diagnostic Groupings of DSDs, Based on Initial Examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Findings</strong></td>
<td><strong>Disorder(s) Suggested</strong></td>
</tr>
<tr>
<td>Presence of uterus</td>
<td>Congenital adrenal hyperplasia (21-OHD) in a virilized female</td>
</tr>
<tr>
<td>Absence of palpable gonads</td>
<td>Gonadal dysgenesis with Y chromosome or true hermaphroditism</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Undervirilized XY male (PAIS or testosterone biosynthetic defect)</td>
</tr>
<tr>
<td>Presence of uterus</td>
<td></td>
</tr>
<tr>
<td>Presence of or a normally sized penis concealed by an abundance of prepubic fat</td>
<td></td>
</tr>
<tr>
<td>Palpable gonads</td>
<td></td>
</tr>
<tr>
<td>Symmetric external genitalia</td>
<td></td>
</tr>
<tr>
<td>Palpable gonads</td>
<td></td>
</tr>
<tr>
<td>Absent uterus</td>
<td></td>
</tr>
</tbody>
</table>

Epithelial cells along the pancreatic ducts secrete bicarbonate that will sustain the neonate until milk feeding is established. Acinar cells secrete digestive enzymes which do not cross the placenta. Insulin stimulates uptake of glucose by muscle and adipose tissue. The fetal pancreas is critically dependent for growth on its own supply of insulin, which does not cross the placenta. Insulin stimulates uptake of glucose by muscle and adipose tissue. The fetal pancreas becomes progressively more responsive to glucose late in gestation, and β-cell mass increases markedly (Dunne et al., 2004). At birth, when maternal glucose supply ceases, the neonate’s blood glucose level declines, along with plasma insulin. A concomitant surge in counter-regulatory hormones epinephrine and glucagon sets in motion the production of glucose that will sustain the neonate until milk feeding is established.

The exocrine portion of the pancreas constitutes 80% of the total gland. Acanin cells secrete digestive enzymes including trypsin, lipase, and amylase into the duodenum. Epithelial cells along the pancreatic ducts secrete bicarbonate and water that neutralize gastric acid.

Disorders of the Pancreas

Rare pancreatic disorders in the newborn include congenital anomalies such as pancreatic agenesis, pancreatic hypoplasia, and annular pancreas. Disorders of the endocrine pancreas include neonatal diabetes mellitus and hyperinsulinism, as well as the developmental disorder of the pancreas seen in the infant of the diabetic mother. The most common newborn disorder of the exocrine pancreas is cystic fibrosis.

Infant of a Diabetic Mother (IDM)

Pathophysiology. If maternal glycemic control is poor in the third trimester, high circulating maternal glucose levels chronically stimulate the fetal pancreas to release insulin, leading to fetal fat deposition. At birth, the neonatal β-cells take time to adjust to the lower circulating glucose level, and continue to secrete insulin, preventing the mobilization of glycogen and fat as sources of glucose. This failure of normal metabolic adaptation places the baby at risk of hypoglycemia.

Excess fetal insulin may also be the cause of delayed maturation of type II alveolar cells and pulmonary surfactant deficiency seen in some IDMs. Transient functional anomalies of the heart, including cardiomyopathy and intraventricular septal hypertrophy, begin in utero with glycogen loading of the septum (Nold & Georgieff, 2004). A delayed adaptation in parathyroid regulation after birth is the source of hypocalcemia and hypomagnesesemia of the IDM. An increase in fetal erythropoiesis leading to polycythemia in the IDM is common but its etiology is unknown. Hyperbilirubinemia results from the presence of an excess hemoglobin, in turn, resulting in a larger than normal bilirubin load.

The higher rate of congenital anomalies associated with diabetic pregnancy is related to maternal glycemic control at the time of conception and during early gestation, when organogenesis is taking place. Congenital malformations associated with maternal diabetes include those of the central nervous system (anencephaly, meningomyelocele, encephalocele, caudal dysplasia), the heart (transposition of the great vessels, coarctation of the aorta, ventricular septal defects, atrial septal defects), the kidneys (hydronephrosis, renal agenesis), and the gastrointestinal tract (duodenal atresia, small left colon syndrome).

Clinical Manifestations. As a result of fat accumulation in late gestation, affected fetuses can develop macrosomia, with birth weights that are not in proportion with their length and head circumference measurements. Intrauterine growth restriction is a less common presentation, seen in advanced maternal diabetic vascular disease. Skin tones may be ruddy with sluggish capillary refill. The neonate may present in respiratory distress. If there is a history of difficult vaginal delivery with shoulder dystocia, the infant may present with musculoskeletal or peripheral nerve findings, suggesting fractured clavicle or humerus or brachial plexus palsy. With the latter condition, the affected arm is held limply at the side, and movements, including Moro responses, are asymmetric. Deep tendon reflexes are absent. Crepitus may be palpated along the clavicle if a fracture is present.

Diagnosis. Macrosomia at birth is a good marker for detecting the infant at risk for neonatal morbidities related to maternal diabetes (Nold & Georgieff, 2004). In spite of the IDM’s size, it is also important to determine gestational age to assess the risk of problems related to prematurity. The IDM must be monitored for hypoglycemia, which usually occurs within an hour or two of birth. Objective measurements of blood and plasma glucose should be used rather than relying on symptoms of hypoglycemia, because the latter are nonspecific and unreliable. Point-of-care blood glucose test results indicating hypoglycemia (<40 mg/dl in the newborn) should be verified with a serum laboratory glucose; however, treatment should not be delayed while awaiting the results of the laboratory test. If no treatment is initiated and the serum glucose is actually higher than the point-of-care glucose, the treatment is relatively benign.

Additional testing required for the IDM is a serum calcium concentration and, if this is low, a serum magnesium.
Hemoglobin level should be measured with a venous, rather than a capillary, blood sample. Additional diagnostic tests will depend on findings of the initial physical examination.

**Pathophysiology.** The fundamental problem in neonatal diabetes mellitus is a failure of the pancreas to release sufficient insulin in response to high blood glucose levels. NDM is unrelated to the presence of anti-insulin or anti-platelet antibodies. In TNDM, diabetes develops within days of birth and resolves again within weeks or months, before recurring, in a milder form, in late childhood. PNDM develops within days to months after birth and persists throughout life. Most cases of PNDM are caused by transcription factors involved in β-cell development and in insulin secretion, the glucose-sensing enzyme glucokinase, and a gene-regulating immune response. The most common genetic causes are activating mutations of enzyme glucokinase, and a gene-regulating immune response. In some infants, insulin therapy can be withdrawn after a period of time when it is observed that exogenous insulin induces hypoglycemia. The course of disease in NDM is highly variable. Some infants with transient NDM will have spontaneous recovery with no further disease recurrence, whereas others will have apparent remission with recurrence of permanent disease in late childhood. Infants with permanent NDM have no remission of their disease.

The opportunity for parents to speak with the pediatric endocrinologist and geneticist should be provided, if possible, for information and guidance about both the cause of NDM and the plans for continuing care for their infant. Close follow-up is essential even if the diabetes has resolved because of the high rate of recurrence later in childhood.

### Neonatal Diabetes Mellitus

**Neonatal diabetes mellitus (NDM)** is a rare disorder manifested by persistent, insulin-sensitive hyperglycemia occurring as early as the first week of life and lasting more than 2 weeks (Sperling, 2005). About half of all cases of NDM are of the transient form (TNDM), and half the permanent form (PNDM).

**Pathophysiology.** Transient neonatal diabetes mellitus is a failure of the pancreas to release sufficient insulin in response to high blood glucose levels. NDM is unrelated to the presence of anti-insulin or anti-platelet antibodies. In TNDM, diabetes develops within days of birth and resolves again within weeks or months, before recurring, in a milder form, in late childhood. PNDM develops within days to months after birth and persists throughout life. Most cases of PNDM are caused by transcription factors involved in β-cell development and in insulin secretion, the glucose-sensing enzyme glucokinase, and a gene-regulating immune response. The most common genetic causes are activating mutations of the K<sub>ATP</sub> channel. Most cases of TNDM are caused by one of three genetic mechanisms: a paternal uniparental isodisomy of chromosome 6, a paternally inherited duplication of 6q24, or a maternal methylation defect within the same region (Sperling, 2005).

**Clinical Manifestations.** A common feature of NDM is intraterine growth restriction, a result of insufficient insulin secretion and subsequent failure to thrive in utero. Intrauterine growth restriction in infants with deficient insulin secretion in utero highlights the importance of insulin as a growth hormone. In addition to being small for gestational age, infants with NDM exhibit hyperglycemia, glycosuria, osmotic polyuria, dehydration, and minimal ketoadidosis.

**Diagnosis.** The diagnosis is made by demonstrating hyperglycemia with low levels of insulin, insulin-like growth factor-1, and C-peptide. The hyperglycemia responds to insulin infusion. Antibodies to insulin or islet cells are absent. If there are signs and symptoms of malabsorption, pancreatic agenesis should be ruled out by abdominal ultrasound. Transient and permanent NDM cannot be differentiated, based on clinical course, in the neonatal period; genetic testing for chromosome 6 anomalies is required (Polak & Shield, 2004).

**Collaborative Management.** Insulin therapy is necessary to manage hyperglycemia and achieve adequate growth, initially by continuous drip and transitioning to subcutaneous injection of an intermediate-acting insulin preparation when condition permits. A high caloric intake can be difficult to maintain. In some infants, insulin therapy can be withdrawn after a period of time when it is observed that exogenous insulin induces hypoglycemia. The course of disease in NDM is highly variable. Some infants with transient NDM will have spontaneous recovery with no further disease recurrence, whereas others will have apparent remission with recurrence of permanent disease in late childhood. Infants with permanent NDM have no remission of their disease.

The opportunity for parents to speak with the pediatric endocrinologist and geneticist should be provided, if possible, for information and guidance about both the cause of NDM and the plans for continuing care for their infant. Close follow-up is essential even if the diabetes has resolved because of the high rate of recurrence later in childhood.

### Congenital Hyperinsulinism

**Congenital hyperinsulinism** is the most frequent cause of severe, persistent hypoglycemia in the newborn. Synonyms for this heterogeneous disorder are hyperinsulinemic hypoglycemia (HH) and persistent hyperinsulinemic hypoglycemia of infancy (PHHI). Several different genetic forms have been described. About 10% to 15% of congenital hyperinsulinism is transient and will spontaneously resolve at 1 month of age (deLonlay et al, 2002). Beckwith-Wiedemann syndrome is a congenital overgrowth syndrome with hyperinsulinism caused by β-cell hyperplasia.

**Pathophysiology.** Hyperinsulinism is due to unregulated insulin release from either the entire pancreas (diffuse β-cell hyperfunction) or from confined areas of the pancreas (focal adenomatous islet-cell hyperplasia). Insulin lowers circulating glucose, suppressing lipolysis and ketogenesis and decreasing the availability of free fatty acids and ketone bodies. Since these are alternative energy substrates for the brain during hypoglycemia, hyperinsulinemia places the infant at risk of severe neurologic dysfunction and seizures as consequences of neuroglycopenia.

**Clinical Manifestations.** Most infants with congenital hyperinsulinism present within the first postnatal days. Generally they are born at term and are normal or large for gestational age. Many are macrosomic with a characteristic facial appearance.

Neonates with Beckwith-Wiedemann syndrome present with a constellation of findings including macroglissia, abdominal wall defects, Wilms’ tumors, renal abnormalities, and facial nevus.

**Diagnosis.** Congenital hyperinsulinism is recognized by severe hypoglycemia with an insulin level that is inappropriate to the level of blood glucose that is present (e.g., an insulin level >5 microunits/ml with a plasma glucose level <50 mg/dl). Diagnostic criteria are a high glucose requirement (>6 to 8 mg/kg/min) needed to maintain normoglycemia, low serum blood glucose by laboratory analysis, measurable insulin, raised C-peptide, low free fatty acids, and low ketone body concentrations. Blood sampling must take place during hypoglycemia to be of diagnostic value (Lindley & Dunne, 2005). The administration of glucagon during hypoglycemia results in a glycemic response.

**Collaborative Management.** The cornerstones of management are a high caloric intake and pharmacologic therapy to inhibit insulin secretion by the pancreas. A central venous catheter is required for reliable and safe administration of high glucose infusates during the acute phase. Glucose infusion rates of 10 to 15 mg/kg/min or higher may be required.
Drugs include diazoxide, which inhibits insulin secretion by blocking the sulfonylurea receptor of the β-cell, and octreotide, which is a somatostatin analogue. Diazoxide must be used with caution in the presence of hypochloraemia because it is highly protein bound and will displace bilirubin from albumin binding sites. Glucagon to mobilize hepatic glucose can be added if needed as a short-term adjunct to therapy (Katz & Stanley, 2005).

Unfortunately, the responsiveness of infants with hyperinsulinism to these agents is inconsistent and variable. Babies who do not show an adequate and immediate response may require pancreatectomy to prevent recurrent neurological symptoms. Preoperative localization procedures and intraoperative biopsies will determine the exact nature of the lesion and how much of the pancreas must be removed. Focal disease may require only a partial pancreatectomy, but a near-total (>95%) removal of the pancreas is indicated for diffuse congenital hyperinsulinism. Loss of the pancreas can pose additional risks such as pancreatic insufficiency and diabetes mellitus.

**Cystic Fibrosis**

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Data from newborn screening programs in the United States reveal that CF occurs in 1 of 2500 to 3700 births overall and is most common among non-Hispanic whites (Grosse et al, 2004).

Pathophysiology. Mutations in the CFTR gene affect the cyclic adenosine-5′-monophosphate (AMP)-mediated signals that stimulate chloride conductance in the epithelial cells of the exocrine ducts. Deficient chloride transport and the associated water-transport abnormalities result in the production of abnormally viscid mucus. Nearly all organs and systems of the body are affected, including the lungs and upper respiratory tract, gastrointestinal tract, pancreas, liver, sweat glands, and genitourinary tract. In the neonate, hyperviscous secretions in the intestines and a deficiency of pancreatic enzymes can combine to create a sticky plug of meconium, a condition known as meconium ileus. The meconium has a higher protein and lower carbohydrate concentration, making it more viscid than normal meconium (Irish, 2003).

Clinical Manifestations. Without a family history or prenatal screening, CF is not recognized at the time of birth in most affected neonates unless a meconium ileus is present. A simple meconium ileus is usually identified at 24 to 48 hours of age (occasionally earlier) when there are signs of intestinal obstruction: abdominal distention, bilious vomiting, and either failure to pass meconium or passage of gray-colored stools. On examination, the dilated loops of bowel have a doughy character that indent on palpation. A complicated meconium ileus has a more dramatic presentation with severe abdominal distention, signs of peritonitis such as tenderness, erythema, and clinical evidence of sepsis. The neonate may be acutely ill and require urgent surgical attention. Although not always present in the neonatal period, most patients with CF have pancreatic enzyme insufficiency and present with digestive symptoms or failure to thrive early in life.

Diagnosis. The possibility of CF is raised in the neonate with meconium ileus, and the diagnosis can be confirmed with DNA testing. A sweat test can also be performed after the first 48 hours of life, if the infant is not edematous (Irish, 2003). A sweat test uses electrical-chemical stimulation of the skin to induce sweat, which is collected and analyzed for chloride content. Newborn screening for CF can be accomplished by measuring immunoreactive trypsinogen in dried blood samples. Screening for CF is now universally offered or mandated in 17 states. CF was named as one of 29 conditions that should be included on all state-mandated newborn screening panels (American College of Medical Genetics, 2004). Sometimes a meconium ileus is identified on prenatal ultrasound as a hyperechoic mass in the terminal ileum, representing inspissated meconium, and dilated bowel loops. Postnatal abdominal radiographs show unevenly dilated bowel and, occasionally, a characteristic “soap bubble” pattern, or small bubbles of gas that are caused by air mixing with the tenacious meconium (Irish, 2003).

Collaborative Management. A meconium ileus requires prompt attention to prevent complications such as volvulus, bowel necrosis, or intestinal perforation. Treatment for simple meconium ileus is a therapeutic Gastrograffin (meglumine diatrizoate) enema performed under fluoroscopy. Gastrograffin is a hyperosmolar, radiopaque solution that evacuates the inspissated meconium from the intestine. Gastrograffin is not used in infants with evidence of volvulus, gangrene, perforation, peritonitis, or atresia of the small bowel. The risks of the procedure are ischemia, hypovolemic shock, and perforation. It is essential to provide adequate hydration to compensate for the rapid fluid losses that can occur with the Gastrograffin enema. It usually takes 24 to 48 hours to evacuate the softened meconium, and serial radiographs are usually ordered to monitor the evacuation. Feedings are started when signs of obstruction have subsided (Irish, 2003). An infant who has undergone a Gastrograffin enema should be observed closely for at least 48 hours for signs and symptoms of perforation of the bowel; late perforation is a rare but possible complication as long as 48 hours after the procedure (Irish, 2003).

Cystic fibrosis is also managed with a diet high in energy and fat to compensate for malabsorption and the increased energy demand of chronic inflammation. In addition to vitamin and mineral supplementation, a hydrolyzed protein formula containing medium-chain triglycerides is used. Medium-chain triglycerides do not require digestion by pancreatic enzymes for absorption. Pancreatic enzyme supplements are also needed to improve fat absorption. Meticulous care of the perianal area must be taken because these enzymes can cause severe perianal dermatitis. Finally, of utmost importance, the care of the neonate with cystic fibrosis requires a team approach, in order to provide the family with the necessary resources and anticipatory guidance to manage this disorder and prevent complications for the best possible outcome.

**SUMMARY**

Some neonatal endocrine disorders are quite rare, and recognizing them requires a high index of suspicion (Palma Sisto, 2004). In recent years, neonatal screening programs have permitted the presymptomatic diagnosis of some of these disorders. This has led to earlier treatment and reduced morbidity, although most endocrine disorders still imply lifelong therapy for the affected infant.
IDENTIFICATION OF THE PROBLEM
A 34-week gestation, 1.33-kg male infant was admitted to the NICU for small size and prematurity. Admission vital signs were HR 128, RR 72, BP 42/23 (mean 30), axillary temperature 97.4° F. Blood glucose screen (point of care) was 104.

A peripheral IV was started with D10W at 80 ml/kg/day (GIR 5.5 mg/kg/min) and the infant was made NPO. A repeat blood glucose screen on D10W was 545. In the belief that this was an error, it was repeated, and the result was 550. A serum glucose level was drawn, and the IV fluids were changed to D5W. The serum glucose was 535. The initial D10W fluid bag was sent to the lab for analysis.

A repeat blood glucose screen on D10W was 550 (serum 632). IV fluids were changed to normal saline, and the repeat blood glucose was 443 (serum 635). An insulin drip was started at 0.05 units/kg/hr and titrated to maintain blood glucose level <250.

DIAGNOSTIC TESTS
The following tests were ordered to further hone in on the cause of hyperglycemia:
- CBC: Hct 42%; WBC 4.4; Segs 20; Bands 8; platelets 274,000
- Blood cultures were negative at 24 and 48 hours.
- Abdominal ultrasound (to rule out pancreatic agenesis): The organ appeared normal.
- Insulin autoantibodies were negative. The insulin drip was stopped for 2 hours and insulin and C-peptide levels were drawn.
- Results: Insulin level <2 micro–international units/ml C-peptide <0.5 ng/ml (reference range 0.8 to 3.1 ng/ml) Concurrent plasma glucose was 412

WORKING DIAGNOSIS
The infant’s presentation at birth and clinical course were most consistent with a diagnosis of neonatal diabetes mellitus. He was intrauterine growth restricted, indicating a prenatal onset of the condition, and he had a mild metabolic acidosis. He had no evidence of autoimmune or structural pancreatic disease. He did not have septicemia or evidence of other infection. Furthermore, his laboratory studies revealed severe insulinopenia. The low level of C-peptide, a single-chain amino acid normally released with insulin in equal amounts, supports this diagnosis. It was not known whether his NDM was transient or permanent; this would require molecular genetic analysis, a test that was not done during the initial hospitalization.

DEVELOPMENT OF MANAGEMENT PLAN
The management plan was to reintroduce glucose while continuing the insulin infusion, advancing to total parental nutrition as tolerated. Glucose levels would be monitored at least every 2 hours, with the goal of keeping the blood glucose <250. The plan included the introduction of feedings as early as feasible to improve control of blood glucose. Continuous insulin would be weaned as tolerated. If his diabetes showed no signs of resolution, subcutaneous insulin would be started for long-term management. The infant would continue to be followed by the pediatric endocrinologist.

IMPLEMENTATION AND EVALUATION OF EFFECTIVENESS
Over the first few days, stabilization of the blood glucose level proved difficult. On TPN, the infant fluctuated between hyperglycemia and hypoglycemia. Feedings were introduced and this provided a measure of stability, although weight gain remained slow. The infant was eventually successfully managed with and discharged on subcutaneous insulin.
REFERENCES


