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Adrenal and Pituitary Insufficiency in the Neonate

David Dempsher, MD, PhD*

Author Disclosure Dr Dempsher did not disclose any financial relationships relevant to this article.

Objectives After completing this article, readers should be able to:

1. Recognize adrenal and pituitary insufficiency in the neonate.
2. Determine the specific cause of the insufficiency state using available endocrine tests and diagnostic imaging.
3. Describe appropriate endocrine replacement therapy.

Abstract
Adrenal and pituitary deficiency can present catastrophically with shock and cardiopulmonary arrest or gradually with lethargy and failure to thrive. Lifesaving treatment is safe and simple, and timely recognition of the disorder minimizes the likelihood of death or permanent brain injury from hypoglycemia and hypothyroidism. This article reviews the major causes and clinical presentations of adrenal and pituitary deficiency states in the newborn period as well as evaluation of pituitary and adrenal function and the principles of endocrine replacement therapy.

Introduction
Most adrenal insufficiency in the neonate results from either hypopituitarism (so-called secondary adrenal insufficiency) or primary adrenal insufficiency due to single-gene defects of adrenal development, steroid biosynthesis, or steroid responsiveness (Table 1). In either case, the presentation can be catastrophic in the first few days after birth, with shock, hypoglycemia, and apnea. Alternatively, signs may develop insidiously over several weeks, with poor feeding, vomiting, and failure to thrive. Acquired adrenal insufficiency may be due to adrenal suppression following fetal or neonatal glucocorticoid exposure. Rarely, adrenal insufficiency is associated with severe bilateral adrenal hemorrhage.

In hypopituitarism, aldosterone secretion is preserved and controlled by the renin-angiotensin system independently of adrenocorticotropic hormone (ACTH). Accordingly, glucocorticoid deficiency may result in shock or hypoglycemia, but hyperkalemia and severe hyponatremia are not seen. Genital anomalies also may distinguish primary from secondary adrenal insufficiency. The 46,XY male who has hypopituitarism may have microphallus and cryptorchidism from fetal gonadotropin deficiency, but the genitalia are not ambiguous. In contrast, some congenital defects of cortisol biosynthesis can cause genital ambiguity because of prenatal androgen biosynthesis that is either excessive in 46,XX girls or deficient in 46,XY boys. A detailed discussion of ambiguous genitalia in the newborn belongs elsewhere, but in this context, the undervirilized or completely feminized 46,XY male may have a proximal adrenal biosynthetic defect such as *StAR* mutation or *3BHSID2* mutation. In North America, a virilized 46,XX female newborn has 21-hydroxylase deficiency until proven otherwise.

Inherited Primary Adrenocortical Insufficiency
Genetic causes of adrenocortical dysgenesis, steroid biosynthesis, and steroid unresponsiveness all have been described. Those likely to present in early infancy with adrenal insufficiency are discussed here.

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Adrenocortical Dysgenesis
At least two genetic causes of adrenocortical dysgenesis are known, and more are likely to be found in the near future. Loss-of-function mutations of \textit{DAX1} cause the syndrome known historically as adrenal hypoplasia congenita, which also is associated with hypogonadotropic hypogonadism. Rare cases of congenital adrenal hypoplasia also have been attributed to mutations of \textit{SF1} (“steroidogenic factor 1”), another gene that, like \textit{DAX1}, encodes a nuclear transcription factor expressed in both the gonads and the adrenal cortex. Deficiency of all adrenal steroids is expected, although not always in the perinatal period.

P450 Side-chain Cleavage Deficiency
In this condition, the side chain of cholesterol is removed to form pregnenolone. Disease-producing mutations of the gene for the enzyme itself (\textit{CYP11A1}) are very rare. The impaired conversion usually is due to mutation of the gene for \textit{StAR}, the “acute steroid regulatory protein” that mediates the transfer of cholesterol across the mitochondrial membrane to the side-chain cleavage enzyme site. The condition is more common among Japanese and Palestinian Arabs. The inability to metabolize cholesterol results in large, lipid-laden adrenals, hence its traditional name “congenital lipoid adrenal hyperplasia.” Concentrations of all classes of adrenal steroids are low in the blood, although surprisingly, salt-wasting adrenal crisis may not present for weeks. The testes also are affected, so 46,XY males appear female or only minimally virilized, perhaps with testes palpable in the labioscrotal folds.

3 Beta-hydroxysteroid Dehydrogenase-2 Deficiency
This enzyme catalyzes conversion of pregnenolone, 17-hydroxypregnenolone, and dehydroepiandrosterone (DHEA) to progesterone, 17-hydroxyprogesterone, and androstenedione, respectively. As expected, mutations of its gene (\textit{HSD3B2}) result in salt-wasting adrenal crisis. The 46,XX female can be mildly virilized because of the peripheral conversion of DHEA to androstenedione by the related enzyme 3 beta-hydroxysteroid dehydrogenase-1, but the 46,XY male is severely undervirilized. The 3 beta-HSD-1 enzyme also can generate diagnostic confusion because systemic blood concentrations of 17-hydroxyprogesterone can be high, although those of the substrates DHEA and 17-hydroxypregnenolone are much higher.
21-hydroxylase Deficiency
Mutations of the 21-hydroxylase gene CYP21 are the most common cause of congenital adrenal hyperplasia in North America. In its classic salt-wasting form, adrenal crisis occurs between 1 and 4 weeks of age, with hyponatremia, hyperkalemia, and shock. 46,XX infants are virilized because the C19 androgen pathway is intact and driven by the elevated ACTH secretion, which, in turn, is driven by the cortisol deficiency and hypovolemia. The 46,XY male may have a large phallus and hyperpigmented scrotum, but historically, many of them died because of delayed diagnosis. Markedly elevated concentrations of the substrate 17-hydroxyprogesterone are virtually diagnostic after 24 to 48 hours of age. Measurements of 17-hydroxyprogesterone now are incorporated in newborn screening programs, facilitating the diagnosis in males.

The 17-hydroxyprogesterone concentration after 24 hours of age usually is diagnostically high in infants who have this condition, but it also is elevated in the preterm infant, which can complicate its interpretation. At 3 days of age in term well newborns, reference 17-hydroxyprogesterone values in 16 infants ranged from 7 to 17 ng/dL in one study and less than 420 ng/dL at “birth to 5 days” in another study. Reference data for preterm infant are shown in Table 2.

Aldosterone Synthase Deficiency
Mutations of CYP11B2 are rare, but they have been described as presenting with hyponatremic hyperkalemic crisis in the infant. This presentation is more likely due to pseudohypoaldosteronism. Glucocorticoid and androgen secretion are predictably normal.

Impaired Steroid Responsiveness
Inherited resistance to either mineralocorticoids or glucocorticoids can cause acute adrenal insufficiency in the young infant. In pseudohypoaldosteronism, salt wasting with hypotension, dehydration, and hyperkalemia is due to either a mutation of the aldosterone receptor gene NR3C2 or of one of the three genes encoding aldosterone’s effector, the epithelial sodium channel. In familial unresponsiveness to ACTH, mineralocorticoid function is normal, but the young infant presents with the hypoglycemia and hypotension of glucocorticoid deficiency. Multiple genes have been implicated as a cause; only in a minority is the ACTH receptor gene itself affected.

Acquired Adrenal Insufficiency
Acquired primary adrenal insufficiency in the newborn is uncommon because the causes in the older child and adult, such as autoimmune disease, adrenoleukodystrophy, and infiltrative and granulomatous diseases, are rare in infancy. One potential cause shared by all ages is secondary adrenal insufficiency from exogenous glucocorticoid suppression. In fact, the fetal adrenal can be suppressed by dexamethasone from the first trimester, but clinical adrenal insufficiency from exogenous glucocorticoid is relatively uncommon. Maternal cortisol and prednisone are metabolized by fetal and placental 11-beta-hydroxysteroid dehydrogenase, preventing even high maternal doses of prednisone from harming the fetus and newborn. Dexamethasone and its isomer betamethasone, however, do cross the placenta to affect the fetus, and these compounds are used therapeutically for this reason. Short courses pre- or postnatally carry little risk. Treatment for longer than 10 to 14 days can result in impaired adrenal function, although seldom are infants symptomatic, even when their cortisol concentrations are low. Routine cortisol replacement usually is not needed. However, any infant who has been given high-dose glucocorticoid for more than 10 to 14 days should be considered at some risk, indicating the need for prompt administration of hydrocortisone for otherwise unexplained hypotension or hypoglycemia or in preparation for surgery.

Adrenal hemorrhage most often is discovered after the fact, with suprarenal calcifications noted incidentally in an asymptomatic infant. Symptomatic bilateral adrenal hemorrhage is seen classically in the large-for-gestational age boy following a difficult delivery or with a coagulopathy. The adrenals usually can maintain normal stress

<table>
<thead>
<tr>
<th>Postconceptional Age (wk)</th>
<th>&lt;30</th>
<th>30</th>
<th>32</th>
<th>34</th>
<th>≥36</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-OHP (ng/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% to 90%</td>
<td>166 to 1,192</td>
<td>119 to 837</td>
<td>126 to 861</td>
<td>73 to 470</td>
<td>98 to 293</td>
</tr>
<tr>
<td>Median</td>
<td>477</td>
<td>407</td>
<td>285</td>
<td>250</td>
<td>170</td>
</tr>
</tbody>
</table>

*23 boys born at 29±1.5 weeks’ gestation, sampled longitudinally after 5 days of age. Data from Al-Saedi et al, 1995.
concentrations of cortisol, even when associated with sepsis, but because the affected infant frequently is hypotensive in these situations, cortisol replacement is prudent, at least until blood cortisol concentrations are measured.

**Diagnosis of Adrenal Insufficiency**

Randomly obtained high concentrations of cortisol are informative, and except in 21-hydroxylase deficiency, effectively exclude glucocorticoid and ACTH deficiency. However, the neonate frequently has values that are diagnostically uninformative, even in the presence of hypoglycemia or hypotension, so a low (<10 mcg/dL [275.9 nmol/L]) random cortisol value is not always diagnostic of primary adrenal disease. Stimulation with either ACTH or glucagon may be helpful. Cortisol concentrations should exceed 15 to 20 mcg/dL (413.8 to 551.8 nmol/L) 1 hour after an intravenous injection of cosyntropin (ACTH1-24) 100 mcg/m² or 2 to 3 hours after administration of intravenous glucagon 50 mcg/kg.

When an enzyme is missing, its substrate’s concentration typically is 20 to 100 times higher than normal. DHEA and 17-hydroxypregnenolone concentrations are very high in 3-beta-hydroxysteroid dehydrogenase deficiency, and 17-hydroxyprogesterone is elevated in 21-hydroxylase deficiency. All the C19 and C21 steroids are low in StAR deficiency and congenital adrenal hypoplasia. Sampling blood 1 hour after administration of cosyntropin 100 mcg/m² and measuring ratios of DHEA to androstenedione and 17-hydroxypregnenolone to 17-hydroxyprogesterone can help in equivocal cases. As in other endocrine receptor disorders, blood aldosterone concentrations are high in pseudohypoaldosteronism.

**Treatment of Acute Adrenal Insufficiency**

Endocrine replacement therapy is safe and potentially lifesaving. The neonatologist should not hesitate to treat the unstable baby empirically, pending definitive diagnosis. Exogenous glucocorticoid can obscure the diagnosis, so when possible, the requisite blood samples should be obtained before empiric therapy is initiated. Intravenous dextrose and normal saline may be needed to maintain systemic perfusion and blood glucose. Intravenous hydrocortisone 50 mg/m² should be administered immediately and maintained at 50 to 100 mg/m² per day in four to six divided doses or by continuous intravenous infusion. High doses of hydrocortisone also have mineralocorticoid activity, but if hyperkalemia or salt wasting ensues, then oral fludrocortisone 0.05 to 0.1 mg is added and continued once daily.

**Hypopituitarism**

Hypopituitarism usually represents a special case of adrenal insufficiency because vascular collapse and hypoglycemia result from impaired ACTH secretion. Occasionally, the newborn who has isolated growth hormone (GH) deficiency also experiences hypoglycemia. (More often, isolated GH deficiency presents with declining linear growth later in childhood.) As with the adrenal, single-gene mutations are known to cause hypopituitarism, although to date, these explain only a minority of cases. Any malformation or injury of the brain affecting the sella or hypothalamus can result in hypopituitarism. The infant who has even minor craniofacial malformations of the midline, such as cleft lip or a single maxillary incisor, is at higher risk for pituitary dysfunction. About 50% of infants who have septo-optic dysplasia, a midline central nervous system malformation involving the optic tracts, also have hypopituitarism.

**Clinical Features That Prompt Evaluation for Hypopituitarism**

Signs of hypopituitarism are nonspecific and shared by other more common conditions in the newborn, so multiple clues usually prompt the diagnostic investigation (Table 3). Hypoglycemia is a cardinal finding, and hypopituitarism should be considered in any infant receiving usual neonatal care who has hypoglycemia after the first 4 to 5 postnatal days. The hypotensive, poorly perfused baby who appears septic, but whose bacteriologic study results are negative, and whose bacteriologic study results are negative and who fails to respond

<table>
<thead>
<tr>
<th>Clinical Findings Associated With Hypopituitarism</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lack of onset or abnormal progression of labor; fetal distress</td>
</tr>
<tr>
<td>• Midline craniofacial or central nervous system defect</td>
</tr>
<tr>
<td>• Unexplained hypotension</td>
</tr>
<tr>
<td>• Nystagmus, optic nerve hypoplasia, and other ocular abnormalities</td>
</tr>
<tr>
<td>• Hypoplastic genitalia in boys</td>
</tr>
<tr>
<td>• Prolonged jaundice; elevated hepatic transaminases</td>
</tr>
<tr>
<td>• Hyponatremia, polyuria</td>
</tr>
<tr>
<td>• Unexplained hypoglycemia</td>
</tr>
<tr>
<td>• Low total thyroxine and inappropriately normal thyroid-stimulating hormone values on newborn screen</td>
</tr>
<tr>
<td>• On magnetic resonance imaging: ectopic posterior pituitary “bright spot,” small anterior pituitary, and attenuated or interrupted pituitary stalk</td>
</tr>
</tbody>
</table>
to empiric antibiotics may have hypopituitarism. Hypothermia, lethargy, poor feeding, prolonged jaundice, and constipation are common and nonspecific symptoms, but they also are common manifestations of hypothyroidism from thyroid-stimulating hormone (TSH) deficiency. Polyuria and hypernatremia may signify antidiuretic hormone deficiency. Impaired prolactin and gonadotropin secretion do not cause acute illness, but the infant boy who has microphallus from gonadotropin deficiency may sicken from ACTH or GH deficiency and, therefore, should be watched and tested. Finally, chance sometimes prods the prepared mind: the diagnosis may occur to the physician when central nervous system imaging obtained for other reasons demonstrates an abnormal pituitary or absent septum pellucidum or the newborn screening result indicates low thyroxine (T4) and inappropriately normal TSH values in a 10-day-old who is cold and feeding poorly for no clear reason.

GH deficiency and gonadotropin deficiency often occur in isolation, but TSH and ACTH deficiency almost never do. If TSH deficiency is demonstrated, the infant must be studied to assess adequate GH and ACTH secretion. Similarly, the baby who has not been exposed to exogenous glucocorticoid and is found to be in adrenal crisis from ACTH deficiency is assumed to be GH- and TSH-deficient until proven otherwise.

Endocrine deficiencies are confirmed readily in the laboratory. In the healthy newborn, plasma concentrations of GH are persistently elevated and should exceed 8 to 15 ng/mL (8 to 15 mcg/L), depending on the assay. The newborn who has hypopituitarism usually has random GH concentrations less than 5 ng/mL (5 mcg/L). (A few weeks after birth, however, GH is secreted only episodically in bursts, so random samples are often uninformative in the older infant, and a stimulation test may be necessary.) In the affected baby, random and stimulated cortisol values are low. Random free T4 measurements are low, and the TSH is inappropriately low or normal (rarely, minimally elevated). Because many sick babies and many stable preterm babies may have low T4 and normal TSH concentrations from sick euthyroid syndrome or other reasons, the low free T4 value usually signifies hypopituitarism only in the context of other typical clinical findings. As noted previously, isolated TSH deficiency is very uncommon, so other pituitary deficiencies should be investigated if secondary hypothyroidism is diagnosed.

Treatment of Hypopituitarism

Hydrocortisone replacement in the sick infant was discussed previously. In the stressed baby, parenteral hydrocortisone at 50 to 100 mg/m² per day should provide adequate glucocorticoid action with little or no risk. Mineralocorticoid replacement is not needed, although hypotension and hypoglycemia may require intravenous dextrose and normal saline. In the stable patient, the daily dose of oral hydrocortisone is about 10 mg/m² per day, administered in three divided doses. GH is administered as a once-daily subcutaneous injection at a dose of 40 mcg/kg per day, and oral levothyroxine at 10 to 15 mcg/kg per day. Hydrocortisone and GH doses usually are adjusted on the basis of body weight or surface area and clinical response. Levothyroxine replacement is adjusted to maintain the blood total T4 or free T4 concentration in the upper half of the normal range by 2 weeks into therapy. The TSH value generally is uninformative in the child who has secondary hypothyroidism.

Hypotension and poor perfusion usually respond to hydrocortisone and normal saline promptly, and lethargy, poor feeding, hypoglycemia, and hypothermia are reversed within a few days. Timely diagnosis and endocrine replacement are urgent because the brain is critically dependent on adequate T4 and glucose for normal development. Unfortunately, the underlying neurologic abnormalities often determine the baby’s outcome, but it behooves the physician to minimize any contribution of postnatal hypothyroidism and hypoglycemia to brain injury.

Suggested Reading


Esoterix Laboratory Services, Inc. Expected Values and SI Conversion Tables. Calabasas Hills, Calif: Esoterix; 2005


Neoreviews Quiz

5. Adrenal insufficiency in the newborn may present catastrophically with shock and cardiopulmonary arrest or gradually with lethargy and failure to thrive. Of the following, the most common cause of adrenal insufficiency in the newborn is:

A. Adrenal hemorrhage.
B. CYP21 gene mutation.
C. Maternal glucocorticosteroid exposure.
D. Steroid acute regulatory protein gene mutation.
E. Steroidogenic factor 1 gene mutation.

6. A term newborn presents with hyponatremic hyperkalemic crisis. Glucocorticoid and androgen secretion are normal. You suspect an enzymatic defect in steroid biosynthesis. Of the following, the most likely enzymatic defect in this infant is a mutation of the gene:

A. CYP11A1.
B. CYP11B2.
C. CYP17.
D. CYP21.
E. HSD3B2.

7. A 6-day-old term newborn has phenotypic features of septo-optic dysplasia, a midline central nervous system malformation involving the optic tracts. You suspect hypopituitarism. Of the following, the laboratory test that is most likely to be uninformative is measurement of:

A. Cortisol.
B. Free thyroxine.
C. Growth hormone.
D. Thyroid-stimulating hormone.
E. Total thyroxine.
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