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Congenital Hypopituitarism as a Cause of Undetectable Estriol Levels in the Maternal Triple-Marker Screen

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We are reporting a child with congenital panhypopituitarism, in whom deficient fetal steroidogenesis was suspected prenatally because of undetectable estriol levels measured in the maternal triple-marker screen. No fetal abnormalities were detected by ultrasonography. Amniocentesis demonstrated a normal 46,XX karyotype. Measurement of maternal urinary steroids failed to show elevation in the excretion of the major precursor for estriol, 16α-hydroxydehydroepiandrosterone, indicating that the fetus did not have steroid sulfatase deficiency (placental sulfatase deficiency), the most common genetic cause of extremely low estriol. The steroid analysis excluded other rare single gene defects, including aromatase deficiency and 17α-hydroxylase deficiency. We therefore suspected that the cause of low estriol in this fetus was adrenal insufficiency. Postnatal evaluation was consistent with panhypopituitarism, characterized by deficiency of all anterior pituitary hormones. Because this screen is now offered to more than half the pregnant women in the United States, reports of low estriol levels have become increasingly common. Therefore, it is essential that physicians be familiar with the various etiologies, perform the appropriate antenatal evaluation to determine the specific cause, and closely monitor both mother and child ante- and postnatally. (*J Clin Endocrinol Metab* 88: 4144–4148, 2003)

THE MATERNAL TRIPLE-MARKER screen is routinely used in standard clinical obstetric practice for the prenatal detection of Down's syndrome and open neural tube defects in women younger than 35 yr (1, 2). It comprises measurement in the second trimester of maternal levels of three serum markers, namely unconjugated estriol (uE_3), α-fetoprotein (AFP), and human chorionic gonadotropin (HCG). Estriol is an estrogen derived from the placental aromatization of fetal androgens of adrenal origin. The production of these androgens is under the control of pituitary ACTH stimulation by the 7th wk of gestation (3). There are very few reports of ACTH deficiency suspected prenatally because of extremely low or undetectable maternal levels of estriol (4, 5). We are reporting a child with congenital panhypopituitarism, whose diagnosis was confirmed postnatally, but in whom undetectable estriol levels in the maternal triple-marker screen led to suspected fetal adrenal insufficiency and alerted us to investigate the newborn child for this condition.

Subject and Methods

Case reports

All studies on this patient were approved by the institutional review board at the New York Presbyterian Hospital. Written informed consent was obtained for all procedures described.

The proposita was delivered, by vacuum extraction for prolonged labor at 39 wk gestation, to a 32-yr-old gravid 2, para 0 mother. The first pregnancy had resulted in a spontaneous miscarriage at 9 wk, the cause of which was unknown. The current pregnancy was remarkable for an abnormal triple-marker screen at 17 wk gestation, which demonstrated an undetectable serum uE_3 level with normal levels of AFP and HCG. A fetal sonogram performed at 20 wk gestation demonstrated normal anatomy and normal growth. There was no evidence of maternal virilization during the pregnancy.

The baby's birth weight (2.850 kg) and length (48.5 cm) were at the 25th percentile, with head circumference (34 cm) at the 10th. Her Apgar scores were 8 and 9 at 1 and 5 min, respectively. Physical examination was consistent with a normal female; no dysmorphic features were present, with the exception of a mildly depressed nasal bridge. Hyperpigmentation was not evident.

The family history was significant for a paternal sibling who had died during the neonatal period, again of unknown cause. There was no consanguinity in the family. Her mother denied drug ingestion during the pregnancy.

Fetoplacental synthesis of estriol during pregnancy

In normal human pregnancy, estrone and estradiol are produced by placental aromatization of both maternal and fetal circulating C_{19} steroids. The third estrogen, estriol, on the other hand, derives almost exclusively from the placental aromatization of the fetal adrenal steroids (Fig. 1) (6). Therefore, measurements of uE_3 levels in the maternal triple screen serve to assess both fetal adrenal and placental function.

The fetal adrenal cortex extracts low-density lipoprotein cholesterol from fetal circulation and converts it to pregnenolone sulfate and dehydroepiandrosterone sulfate (DHEAS) (Fig. 1). Early in pregnancy, DHEAS is produced by the fetal adrenal gland independent of pituitary ACTH stimulation, whereas, by the latter part of the first trimester, ACTH is required for adrenal function. DHEAS is then hydroxylated in the fetal liver by the 16α-hydroxylase enzyme (P450 3A7) to form 16α-hydroxydehydroepiandrosterone sulfate (16-OH-DHEAS). In the placenta, the sulfate group of 16-OH-DHEAS is cleaved by the steroid sulfatase enzyme, forming the unconjugated steroid, 16α-hydroxydehydroepiandrosterone (16-OH-DHEA), which is then converted to estriol in a series of steps that involves the 3β-hydroxysteroid dehydro-

Abbreviations: AFP, α-Fetoprotein; CAH, congenital adrenal hyperplasia; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; HCG, human chorionic gonadotropin; LAH, lipoid adrenal hyperplasia; 16-OH-DHEAS, 16α-hydroxydehydroepiandrosterone sulfate; 16-OHAn, 16α-hydroxyandrosterone; 16-OHEt, 16α-hydroxyetiocholanolone; 17-OHP, 17α-hydroxyprogesterone; PRL, prolactin; SLOS, Smith-Lemli-Opitz syndrome; StAR, steroidogenic acute regulatory protein; STS, steroid sulfatase deficiency, uE_3, unconjugated estriol.

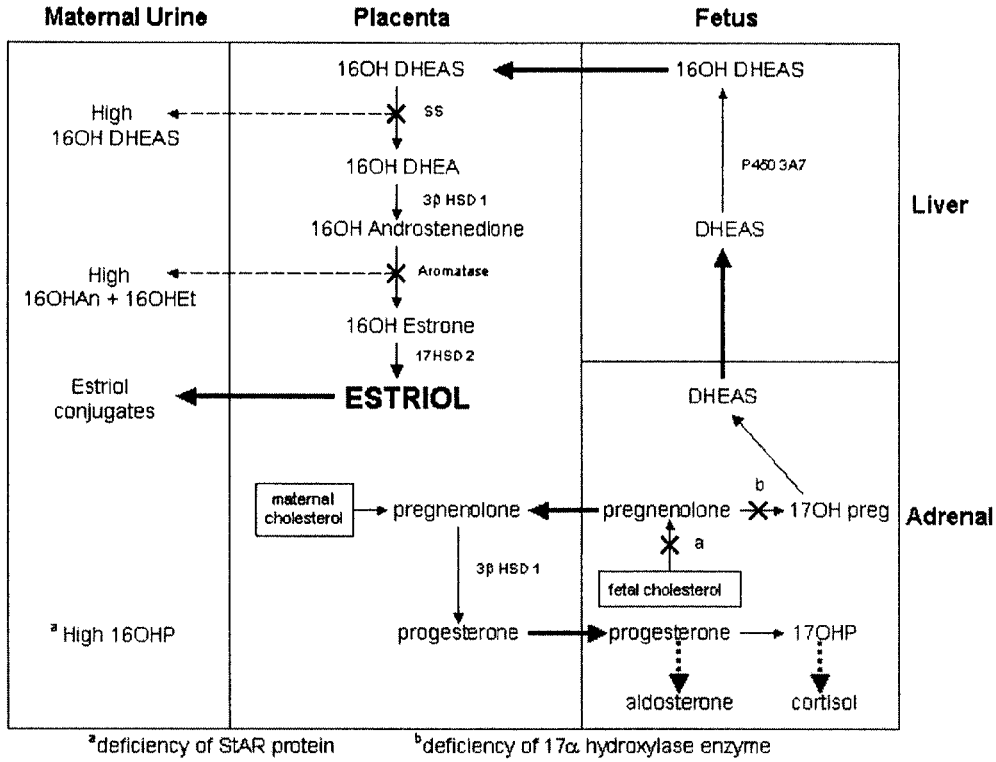

FIG. 1. The synthesis of estriol by the fetoplacental unit during pregnancy. Various enzyme defects (indicated by an X) are associated with elevation of specific maternal urinary steroid metabolites. It is important to note that, although pregnenolone can be used directly as a substrate for the production of C_{19} steroids by the fetal adrenals, the functional absence of the 3β-hydroxysteroid dehydrogenase enzyme prevents direct conversion of pregnenolone to progesterone, at least in the dominant fetal zone. In a pregnancy with a fetus affected by 17α-hydroxylase deficiency, the large amounts of fetal adrenal pregnenolone are metabolized in the fetal liver and the placenta, ultimately being converted into 16α-hydroxypregnanolone by the maternal liver. 17OH preg, 17α-hydroxypregnanolone; 16OH DHEA, 16α-hydroxydehydroepiandrosterone; 16OH Androstenedione, 16α-hydroxyandrostenedione; 16OH Estrone, 16α-hydroxy estrone; 16OHAn, 16α-hydroxyandrosterone; 16OHP, 16α-hydroxypregnanolone. SS, steroid sulfatase enzyme; 3β HSD 1, 3β hydroxysteroid dehydrogenase type 1; 17HSD 2, 17β hydroxysteroid dehydrogenase type 2; P450 3A7, 16α-hydroxylase; X, enzyme deficiency. [Adapted from Ref. 6.]

genase type 1, aromatase and 17β-hydroxysteroid dehydrogenase type 2 enzymes (7). From the second trimester, 90% of estriol production is accounted for by DHEAS derived from the fetal adrenal glands. The majority of the estriol (>90%) is secreted into the maternal circulation, where it can first be detected at 9 wk and peaks at 31–35 wk gestation (6). It is metabolized in the maternal liver and excreted in the urine principally in the conjugated form. Approximately 10% of the estriol remains in the maternal circulation in the unconjugated form (uE_3) (7).

Differential diagnosis

Marked reduction in uE_3 with normal AFP and HCG levels during the second trimester is most commonly associated with early fetal death and anencephaly (Table 1) (1). Rarely, extremely low uE_3 levels in the maternal triple-marker screen are caused by placental defects or defects in fetal adrenal steroidogenesis. Maternal ingestion of corticosteroids must also be considered, because dexamethasone can cross the placenta and suppress the fetal adrenal glands (8, 9). Finally, ACTH deficiency, isolated or in combination with deficiency of other anterior pituitary hormones, as well as ACTH insensitivity (such as familial glucocorticoid deficiency) can result in insufficient production of fetal adrenal steroids and, therefore, in extremely low uE_3 levels.

Steroid sulfatase deficiency (STS) is the prenatal manifestation of recessive X-linked ichthyosis, a condition that affects about 1 in 3000 males (10). Deficiency of this enzyme prevents conversion of precursors to estriol (Fig. 1). STS is, therefore, biochemically characterized by very low or undetectable estriol levels, in combination with elevation of the Δ^5 estriol precursors such as 16-OH-DHEAS, in amniotic fluid and in maternal serum and urine (11). A less common cause of low estriol is placental aromatase deficiency, which results in a build-up of 16α-hydroxyandrostenedione and other androgens (Fig. 1). Maternal virilization is often evident in this condition, with masculinization of the female fetus (12, 13).

TABLE 1. The causes of extremely low uE_3 levels in the maternal triple-marker screen

Fetal death
Anencephaly
Placenta
Steroid sulfatase deficiency
Aromatase deficiency
Fetal
Adrenal
SLOS
LAH
17α-Hydroxylase deficiency
X-linked CAH
Pituitary
ACTH deficiency
ACTH insensitivity syndromes
Maternal
Ingestion of corticosteroids

Intrinsic defects in fetal adrenal steroidogenesis, which result in extremely low estriol levels, such as lipoid adrenal hyperplasia (LAH) and 17α-hydroxylase deficiency, as well as X-linked congenital adrenal hypoplasia, are all characterized by the inability of the fetal adrenals to produce DHEAS. On the other hand, deficiency of the 21-hydroxylase or the 11β-hydroxylase enzymes resulting in these two forms of congenital adrenal hyperplasia (CAH) allows fetal adrenal production of

DHEAS. In fact, both forms of CAH would be expected to produce increased amounts of fetal DHEAS, resulting in elevated estriol levels.

Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive disorder of cholesterol biosynthesis that is caused by loss-of-function mutations in the *DHCR7* gene. This gene encodes the enzyme, 7-dehydrocholesterol-Δ-7-reductase, that catalyzes the final step in cholesterol biosynthesis (14). SLOS occurs at a population-dependent frequency of 1 in 15,000–20,000 live births (15), although the number of affected fetuses may be much higher, with prenatal death being common. Deficiency of the enzyme results prenatally in reduced estriol levels secondary to cholesterol deficiency (16). It is also notable for having a unique equine-type estriol in maternal urine, which can be used as a diagnostic analyte (17, 18). Clinically, it is manifested postnatally by multiple congenital anomalies and mental retardation. Adrenal insufficiency in newborns and infants is only evident in the most severe cases.

LAH is a rare and severe form of CAH in which cholesterol accumulates in steroidogenic cells as a result of the failure to convert cholesterol to pregnenolone. This leads to the inability to synthesize all adrenal and gonadal steroids, producing phenotypic females with severe salt loss. Though a defect in the enzyme for mitochondrial cholesterol side chain cleavage, known as cytochrome P450scc, was previously thought to be the cause of LAH, until recently no mutations of its gene had been found. Most of the patients initially genotyped were actually found to have mutations of the gene encoding the steroidogenic acute regulatory protein (StAR), which facilitates the transport of cholesterol into the mitochondria. Recently, a heterozygous mutation of P450scc has been identified in a patient with LAH and normal StAR genes (19). Deficiency of the 17α-hydroxylase enzyme, which is also expressed in the adrenal cortex and testes, produces another rare form of CAH, characterized by decreased synthesis of glucocorticoid and sex steroids (Fig. 1) and resulting in 46,XY males with a female sexual phenotype at birth (20). Diagnosis is rarely achieved at birth, and the condition often is not suspected until there is a lack of pubertal maturation. Because 17α-hydroxylation is not required for synthesis of mineralocorticoids, salt losing does not occur; and indeed, these subjects are typically hypertensive, probably because of excess synthesis of the mineralocorticoid, deoxycorticosterone.

X-linked congenital adrenal hypoplasia results from mutations in the *DAX-1* gene located on chromosome Xp21, which encodes a nuclear hormone receptor with a novel DNA-binding domain (21). This disorder, which occurs with a frequency of 1 in 12,500 births (22), produces primary adrenocortical failure commonly accompanied by hypogonadotropic hypogonadism. Sixty percent of affected boys typically present in early infancy with salt wasting secondary to adrenal failure, whereas the remainder are diagnosed during childhood (23). The age at which hypogonadotropic hypogonadism is diagnosed is also variable, ranging from birth to adolescence with the failure of pubertal development (23).

Congenital hypopituitarism, characterized by the deficiency of 2 or more anterior pituitary hormones, is rare, with an incidence of 1 in 100,000 live births (24). Its causes include birth trauma and/or asphyxia, which results in disruption of the pituitary stalk, midline defect syndromes, and mutations of genes encoding pituitary transcription factors (25). These transcription factors, which include POU1F1 (formerly referred to as Pit-1), PROP1, HESX1, and LHX3/LHX4, direct the embryonic development of the anterior pituitary gland. In humans, mutations of *POU1F1* result in deficiency of GH, prolactin (PRL), and TSH; ACTH and gonadotropins are spared (26). Mutation of *PROP1* causes deficiency of GH, PRL, and TSH, as well as the gonadotropins. ACTH is spared initially, but there is a tendency toward the development of deficiency with age (26). Mutations of *HESX1* (also referred to as *RPX*), a pituitary transcription factor that also plays a role in the development of the optic nerves, has been implicated in septooptic dysplasia. This is a heterogeneous disorder characterized by midline neurological abnormalities associated with pituitary hypoplasia and optic nerve hypoplasia (27). Mutations in *LHX3* have been identified in humans with abnormal neck and cervical spine development in whom deficiency of all anterior pituitary hormones, except for ACTH, occurs (28). Mutations have been identified in *LHX4* in a family with GH, TSH, and ACTH deficiency in combination with cerebellar and skull-base malformations (29).

Results

Prenatal evaluation

After the undetectable estriol level was reported in the maternal triple-marker screen, amniocentesis was performed at 30 wk gestation. Chromosomal analysis demonstrated a normal 46,XX karyotype. Steroid hormone analysis of the amniotic fluid, by RIA after separation by chromatography, demonstrated reduced levels of 17α-hydroxyprogesterone (17-OHP), Δ^5 and Δ^4 steroids, as well as cortisol (Table 2).

Analysis of steroids in maternal urine by gas chromatography-mass spectrometry was undertaken at the 28th and 34th wk of gestation to confirm and to investigate causes of the low estriol production (Table 3) (11, 30). Deficiency of estriol is illustrated by its low excretion, relative to the other major metabolite of pregnancy, pregnanediol. Pregnanediol, the primary urinary metabolite of placental progesterone, is ultimately derived from circulating maternal cholesterol, so that the fetus does not contribute precursors to its formation. Because the production of progesterone increases roughly 100-fold, and estriol 1000-fold, during normal pregnancy, the estriol:pregnanediol ratio gradually increases. Notably, analysis of maternal urine showed a decrease in the estriol:pregnanediol ratio between the first sample at the 28th wk and second sample at the 34th wk gestation, indicating inadequate estriol production (Table 3).

A profile of excreted compounds has been developed to distinguish some of the single-gene defects responsible for extremely low estriol (11). These diagnoses are based on ratios of urinary metabolites that are expected to be radically altered by the presence of any of the conditions known to cause low estriol. The results listed in Table 3 are as follows: 1) STS is normally demonstrated by markedly increased excretion of 16-OH-DHEAS and related compounds. It is represented by the ratio of 16-OH-DHEA:estriol (before analysis, the sulfate is removed from 16-OH-DHEAS). This ratio was not increased in this patient. 2) Aromatase deficiency should result in the increased excretion of metabolites of 16α-hydroxyandrostenedione, the immediate precursor steroid for aromatase. Two such metabolites are 16α-hydroxyandrosterone (16-OHAn) and 16α-hydroxyetiocholanolone (16-OHEt). Increased excretion of these metabolites could be determined by measurement of 16-OHAn + 16-OHEt:estriol or by employing another androsterone metabolite as a denominator, *i.e.* one that is not related to pregnancy, such as 11β-hydroxyandrosterone. These ratios were not increased for the samples analyzed. 3) For 17α-hydroxylase deficiency, in the absence of 16-OH-DHEA (a C_{19} steroid), increased production of 16α-hydroxypregnenolone, a

TABLE 2. Steroid hormone analysis of amniotic fluid at 30 wk gestation, demonstrating reduced levels of 17-OHP, Δ^5-17-hydroxypregnenolone, DHEA, Δ^4-androstenedione, and F

Steroid hormone	17-OHP ng/dl	17Δ^5P ng/dl	DHEA ng/dl	Δ^4A ng/dl	F μg/dl
Result	12	11	9	3	2.6
Normal Range (31)	22–109	30–140	32.9	29–37	4–11

17Δ^5P = Δ^5-17-hydroxypregnenolone, Δ^4A = Δ^4-androstenedione, F = cortisol.

TABLE 3. Maternal urine diagnostic parameters

Disorder	Diagnostic ratios	Patient		Normal[b]	Affected[c]
		28 wk[a]	34 wk[a]		
Estriol deficiency	Estriol:pregnanediol	0.021	0.013	0.48 (0.28–0.78)	<0.2
Steroid sulfatase deficiency	16-OH-DHEA:estriol	0.37	0.18	0.15 (0.07–0.3)	30 (2.1–111)
Aromatase deficiency	16-OHAn+16-OHEt:estriol	0.085	0.061	0.05 (0.03–0.024)	>10
	16-OHAn:11-OHAn	0.045	0.037	0.28 (0.1–0.42)	>10
17α-Hydroxylase deficiency	16-OHP:16-OHAn+16-OHEt	2.34	3.80	1.26 (0.47–2.99)	>10
Adrenal insufficiency	Pregnanetriol:pregnanediol	0.042	0.019	0.1 (0.05–0.2)	<0.05
SLOS[d]	8-DH estriol:estriol	<0.005	<0.005	<0.015	0.86 (0.07–1.38)

Estriol deficiency is characterized by reduction in the estriol:pregnanediol ratio. Diagnostic ratios for specific causes of estriol deficiency are then listed. 8-DH estriol, 8-Dehydroestriol.

[a] Gestational age at time of maternal urine collection.

[b] The values given (mean and range) were obtained from pregnancies at a lower gestational age (15–25 wk). Most ratios would not be expected to change significantly with increasing gestational age.

[c] Measured (mean and range) or predicted values for patients carrying a fetus with listed disorders (n = 30 for STS deficiency and 5 for SLOS).

[d] This diagnostic parameter was not available at time of diagnosis.

C_{21} steroid and the metabolite of fetal pregnenolone, would be expected. 16α-Hydroxypregnenolone would be converted to 16α-hydroxyprogesterone in the placenta and reduced to 16α-hydroxy-pregnanolone (by the 5β-reductase and 3α-hydroxysteroid dehydrogenase enzymes) in the maternal liver. Thus, the ratio in maternal urine of 16α-hydroxypregnanolone metabolites (C_{21} steroids):16α-hydroxy androgens (C_{19} steroids) should be greatly increased. This was determined through the 16α-hydroxypregnanolone:16-OHAn + 16-OHEt ratio which was not significantly increased, indicating the fetus did not have 17α-hydroxylase deficiency. 4) The pregnanetriol:pregnanediol ratio was reduced, compared with normal, which should indicate adrenal insufficiency, because about half of maternal urinary pregnanetriol, the major 17-OHP metabolite, originates in the fetus. This was consistent with the low 17-OHP concentration in the amniotic fluid (Table 2). 5) At the time of this study, specific urinary diagnostic analytes for SLOS (17, 18) had not been discovered, but we have measured them retroactively. One of the diagnostic ratios is the excretion of 8-dehydroestriol, relative to that of estriol, and these values were normal.

Postnatal evaluation and course

A standard Cortrosyn stimulation test (ACTH, 250 μg, by iv bolus) on the 4th day of life demonstrated a negligible baseline serum cortisol of 0.2 μg/dl, with minimal rise on stimulation to 2.9 μg/dl. A plasma ACTH level of 6 pg/ml was inappropriately low for this cortisol level. The baseline plasma aldosterone level was normal at 11 ng/dl.

In the neonatal period, the baby experienced multiple hypoglycemic episodes, which persisted despite glucocorticoid therapy. A GH level measured at less than 1.5 ng/ml during a hypoglycemic episode (plasma glucose of 30 mg/dl) was consistent with GH deficiency. The hypoglycemia resolved with initiation of GH therapy. Further endocrine evaluation revealed deficiency of gonadotropins, TSH, and PRL. There was no clinical evidence of diabetes insipidus. A magnetic resonance imaging of the brain demonstrated a normal anterior pituitary gland with a normally positioned posterior bright spot, as well as a normal and intact pituitary stalk. A sonogram showed hypoplastic adrenal glands measuring 1.0 cm in length on the right and 1.1 cm in length on the left. There were no focal lesions within the adrenal glands.

Based on this patient's hormonal phenotype, we undertook a molecular genetic evaluation of those candidate transcription factor genes most likely to be pathologically involved, including *PROP1*, *HESX1*, and *LHX4*. No definitive mutations were identified in any of these genes.

Discussion

During this pregnancy, deficient fetal steroidogenesis was suspected because of the marked reduction in estriol in maternal serum, urine, and amniotic fluid, together with lack of elevated urinary excretion of markers for other conditions known to attenuate estriol production. Placental sulfatase deficiency was excluded because of the absence of elevation of Δ^5 steroid precursors, and a normal 46,XX karyotype. Fetal sonography did not reveal anencephaly or fetal death, and there was no aneuploidy on chromosomal analysis. Her postnatal evaluation was consistent with congenital hypopituitarism, with an unusual pattern of deficiency affecting all anterior pituitary hormones, including ACTH.

Because the maternal triple screen is becoming standard practice in routine antenatal care with more than half of pregnant women participating in the United States, we predict an increase in the number of pregnancies reported with marked reduction in uE_3 levels. After the common etiologies are excluded, which should always include a detailed history of maternal drug intake, it is essential that disorders of the fetal adrenal glands be considered. A multidisciplinary approach is crucial for proper evaluation of the fetus and mother, as well as placental function, and should include appropriate analysis of maternal urine or amniotic fluid. Though some disorders do not pose a serious health risk, certain are life threatening, and such pregnancies should be managed in high-risk centers with participation by neonatal intensivists, pediatric endocrinologists, and geneticists. Prompt evaluation and appropriate therapy must be instituted to avoid episodes of hypoglycemia or salt wasting that could lead to significant permanent neurological sequelae and even death if not recognized and adequately treated.

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Erratum

In the article "Dehydroepiandrosterone Supplementation and Bone Turnover in Middle-Aged to Elderly Men" (*The Journal of Clinical Endocrinology & Metabolism* **87:** 1544–1549), the names of two authors, Owen Wolkowitz and Louann Brizendine (Department of Psychiatry, University of California, San Francisco, California 94143), were omitted. The list of authors in order is Arnold J. Kahn, Bernard Halloran, Owen Wolkowitz, and Louann Brizendine.