

PEDIATRICS®

Low Estriol Levels in the Maternal Triple-Marker Screen as a Predictor of Isolated Adrenocorticotrophic Hormone Deficiency Caused by a New Mutation in the TPIT Gene

Naomi Weintrob, Jacques Drouin, Sophie Vallette-Kasic, Ellen Taub, Daphna Marom, Yael Lebenthal, Gil Klinger, Efrat Bron-Harlev and Mordechai Shohat
Pediatrics 2006;117;322-327; originally published online Jan 3, 2006;
DOI: 10.1542/peds.2005-1973

This information is current as of February 22, 2006

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/117/2/e322>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2006 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Low Estriol Levels in the Maternal Triple-Marker Screen as a Predictor of Isolated Adrenocorticotrophic Hormone Deficiency Caused by a New Mutation in the *TPIT* Gene

Naomi Weintrob, MD^{a,b}, Jacques Drouin, PhD^c, Sophie Vallette-Kasic, MD, PhD^c, Ellen Taub, MSc^d, Daphna Marom, MD^d, Yael Lebenthal, MD^a, Gil Klinger, MD^{b,e}, Efrat Bron-Harlev, MD^{b,f}, Mordechai Shohat, MD^{b,d}

^aInstitute for Endocrinology and Diabetes, ^bNeonatal Intensive Care Unit, and ^cPediatric Intensive Care Unit, Schneider Children's Medical Center of Israel, Petah Tiqwa, Israel; ^dSackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ^eInstitut de Recherches Cliniques de Montréal, Laboratoire de Génétique Moléculaire, Montreal, Quebec, Canada; ^fDepartment of Medical Genetics, Rabin Medical Center, Beilinson Campus, Petah Tiqwa, Israel

The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

Isolated adrenocorticotrophic hormone (ACTH) deficiency (IAD) is a rare cause of adrenocortical insufficiency, especially in children, and may be an underestimated cause of neonatal death. Early postnatal diagnosis may prevent hypoglycemic seizures, Addisonian crises, and death. There are also occasional reports of prenatal diagnosis of IAD by findings on the maternal triple-marker screen (TMST), a combined serum analyte test that measures levels of α -fetoprotein, human chorionic gonadotropin, and unconjugated estriol for the detection of Down syndrome and open neural-tube defects. An isolated low estriol level is usually correlated with compromised uteroplacental perfusion and frequently associated with fetal death. A low estriol level in the context of normal fetal sonography and growth, after exclusion of placental sulfatase deficiency and Smith-Lemli-Opitz syndrome, should raise the suspicion of deficient fetal steroidogenesis, which leads to decreased production of adrenal dehydroepiandrosterone sulfate.

We describe 2 brothers with adrenal insufficiency resulting from IAD. The parents are first cousins whose first son is healthy. During the pregnancy of the second son, who died at the age of 7 weeks as a result of presumed cardiomyopathy, a low estriol level on the TMST was ignored because of a normal fetal ultrasound. In the third pregnancy, a low level was found again, and the mother was referred to our tertiary center. Ultrasonography revealed no abnormalities, and karyotype was normal. Normal levels of steroid sulfatase activity and 7-dehydrocholesterol ruled out X-linked ichthyosis and Smith-Lemli-Opitz syndrome, respectively. Postnatally, basal and stimulated cortisol and ACTH levels were low. Other pituitary functions were normal, suggesting the diagnosis of IAD. The patient was treated with a stress dose of hydrocortisone on day 2 of life, which was tapered to a maintenance dose. At the time of this writing, he was 7 months old, with normal growth and development.

Recently, loss-of-function mutations in the human *TPIT* gene were detected in autosomal recessive IAD. *TPIT* is a cell-restricted T-box transcription factor that is important for the terminal differentiation of pituitary corticotrophs.

Key Words: ACTH deficiency, neonate, estriol, TPIT

Abbreviations: ACTH, adrenocorticotrophic hormone; IAD, isolated ACTH deficiency; TMST, maternal triple-marker screen; AFP, α -fetoprotein; hCG, human chorionic gonadotropin; MoM, multiples of the median; 17-OHP, 17 α -OH-progesterone; GH, growth hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulfate; TSH, thyroid-stimulating hormone; FT4, free thyroxine; PCR, polymerase chain reaction

www.pediatrics.org/cgi/doi/10.1542/peds.2005-1973

doi:10.1542/peds.2005-1973

Accepted for publication Sep 17, 2005

Address correspondence to Naomi Weintrob, MD, Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, Petah Tiqwa 49202, Israel. E-mail: nweintrob@clalit.org.il

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2006 by the American Academy of Pediatrics

Therefore, we performed molecular analysis of the *TPIT* gene, which revealed a new mutation (IVS4+1G>A) that affects the first nucleotide of the splice site at the 5' end of the fourth intron. This stop codon probably leads to loss of *TPIT* function by nonsense-mediated mRNA decay, as it does for other *TPIT* nonsense mutations.

We recommend that pregnant women with an isolated low estriol level of unexplained etiology be referred for additional evaluation by a multidisciplinary team that includes a geneticist and pediatric endocrinologist. Prompt ACTH testing in the first postnatal days will allow for early diagnosis. The immediate institution of glucocorticoid therapy, with proper instructions for stress management, can prevent unnecessary neonatal death secondary to an easily treatable disease.

ISOLATED ADRENOCORTICOTROPIC HORMONE (ACTH) deficiency (IAD) is a rare cause of adrenocortical insufficiency, especially in children, and may be an underestimated cause of neonatal death.¹ Early postnatal diagnosis may prevent hypoglycemic seizures, Addisonian crises, and death. Prenatal diagnosis by low maternal levels of estriol has occasionally been reported.^{2,3}

The maternal triple-marker screen (TMST) is a combined serum analyte measurement that is used routinely in standard clinical obstetric practice for the prenatal detection of Down syndrome and open neural-tube defects.⁴ The screening test measures the levels of α -fetoprotein (AFP), human chorionic gonadotropin (hCG), and unconjugated estriol. Estriol is an estrogen derived from the placental aromatization of fetal adrenal androgens. By the seventh week of gestation, the production of these androgens is controlled by pituitary ACTH stimulation⁵; therefore, low levels of fetal adrenal androgens caused by primary or secondary adrenal insufficiency can lead to low maternal estriol levels. It is extremely important that infants born to mothers with low estriol levels of unexplained cause undergo prompt postnatal evaluation to rule out adrenal insufficiency, because deteriorating adrenal function that leads to neonatal death frequently follows an asymptomatic period. Early initiation of glucocorticoid therapy with proper instructions for stress management is life saving.

Here we report on 2 brothers in whom low estriol levels were detected during pregnancy by the TMST. Adrenal insufficiency was strongly suspected during the pregnancy of the second brother because of the history of neonatal death of the older sibling. Furthermore, the low maternal serum estriol levels could not be accounted for by fetal death, uteroplacental compromise, anencephalic fetus, steroid sulfatase deficiency, or Smith-Lemli-Opitz syndrome.

SUBJECTS AND METHODS

The parents, who were first cousins of Jewish-Indian origin, were referred for genetic consultation because of a low serum estriol level detected in the TMST conducted at 17 weeks' gestation, with normal levels of AFP and hCG. The mother was 38 years old, gravida 3, para 2. The first-born son was healthy and 5 years old at the time. The estriol level during that pregnancy was within the normal range (1.03 multiples of the median [MoM]; reference: >0.15 MoM). The mother's medical history revealed mild gestational diabetes mellitus that was controlled by diet alone in the second and third pregnancies. The father was 45 years old and healthy.

The family history was remarkable for type 2 diabetes, hypertension, hypercholesterolemia in the maternal grandmother, and hemolytic anemia diagnosed at 70 years of age and treated by steroids in the paternal grandmother. There was no history of early neonatal death or glucocorticoid treatment in the extended family. During the couple's second pregnancy, a low estriol level of 0.09 MoM was noted on the TMST. The levels of AFP and hCG were normal, and a fetal sonogram performed at 20 weeks' gestation demonstrated normal anatomy of a male fetus and normal growth. After an uncomplicated prenatal course, a normal-appearing male infant weighing 2320 g with a head circumference of 33 cm was delivered in another hospital at 38 weeks' gestation. Apgar scores were 9 and 10 at 1 and 5 minutes, respectively, and physical examination was unremarkable. During the first day of life, the infant had an episode of hypoglycemia (blood glucose level: 34 mg/dL), which was considered secondary to the maternal gestational diabetes mellitus and treated with intravenous glucose. He also had hyponatremia (sodium: 127 mEq/L), which resolved spontaneously, and a normal potassium level of 5 mEq/L. The child was discharged from the hospital on the 10th day of life weighing 2450 g. He was readmitted at the age of 7 weeks because he had a fever of 38.5°C, symptoms of upper respiratory infection, and jaundice. Physical examination revealed normal vital signs, jaundiced skin and sclera, a mild systolic murmur, and mild splenomegaly. On laboratory evaluation, direct hyperbilirubinemia was found; extensive workup for infectious or metabolic causes was negative. Echocardiography revealed a dilated left ventricle, moderate mitral regurgitation, and decreased left heart function. The infant died of multiorgan failure at the age of 7 weeks. The presumed diagnosis was cardiomyopathy or myocarditis. The parents declined a postmortem examination.

The low estriol level detected in the third pregnancy (0.14 MoM; reference: >0.15 MoM) prompted the parents to seek genetic consultation, and they were referred to our hospital.

Informed consent was obtained from the parents for the genetic evaluation as part of the clinical investiga-

tion. Because this article deals only with clinical description, there was no need for local institutional review board approval.

Laboratory Investigations

An ACTH-stimulation test was performed with an intravenous injection of 62.5 μg of ACTH-1-24 (Synacthen; Ciba-Geigy, Basel, Switzerland). Blood samples for cortisol and 17 α OH-progesterone (17-OHP) determination were drawn at 0 and 60 minutes, and for ACTH, blood samples for plasma renin activity, thyroid function, growth hormone (GH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), dehydroepiandrosterone sulfate (DHEAS), and testosterone levels were drawn at time 0. Measurements were performed by chemiluminescent immunometric assay by using Immulite 2000 (cortisol, ACTH, GH, thyroid-stimulating hormone [TSH], free thyroxine [FT4], FSH, and LH; DPC, Los Angeles, CA) or by radioimmunoassay by using commercial kits (testosterone, DHEAS: DPC, Los Angeles, CA; 17OHP: MP Biomedicals, Orangeburg, NY; plasma renin activity: DiaSorin, Stillwater, MN).

Genetic Analysis of the *TPIT* Gene

Genetic analysis of the *TPIT* gene was performed by the 2 authors (S.V.-K. and J.D.) in Montreal. DNA was extracted from peripheral lymphocytes and amplified by polymerase chain reaction (PCR) using 8 sets of flanking intronic primers for direct sequencing of exons. The primer sequences were described by Pulichino et al.⁶ Amplification was conducted in a 50-mL reaction using 200 ng of genomic DNA, 250 ng of each primer, and the Vent polymerase as described previously.⁶ PCR products were purified on agarose gel by using the Qiagen GmbH (Hilden, Germany) gel-extraction kit. Internal primers were used for sequencing by using a CEQ 2000 sequencer from Beckman-Coulter (Fullerton, CA). The mutation was confirmed by repeat PCR and subsequent sequencing of PCR products.

RESULTS

During the pregnancy with the third child, there was no evidence of maternal virilization. Ultrasonography revealed no fetal abnormalities, and the genitalia appeared to be normal male. Amniocentesis demonstrated a normal 46,XY karyotype. The level of steroid sulfatase activity in amniotic cell culture ruled out the diagnosis of X-linked ichthyosis, and the normal amniotic fluid level of 7-dehydrocholesterol (0.05 $\mu\text{g}/\text{mL}$; reference: < 0.9 $\mu\text{g}/\text{mL}$) ruled out Smith-Lemli-Opitz syndrome.

The infant was born at 40 weeks' gestation, weighed 2940 g, had a head circumference of 35 cm, and had Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. Physical examination was consistent with a normal male; no dysmorphic features were present, and

there was no evidence of hyperpigmentation or micropenis. Glucose and electrolyte levels were consistently normal on serial testing. The hormone profile of the infant is shown in Table 1. The ACTH-stimulation test that was performed on the second day of life yielded low basal and stimulated cortisol levels (<27.6 and 58 nmol/L, respectively), low levels of 17-OHP for age (basal: 3.5 nmol/L; stimulated: 8.1 nmol/L), and undetectable ACTH and DHEAS levels (<2.2 pmol/L and <0.41 $\mu\text{mol}/\text{L}$, respectively), which is consistent with the diagnosis of secondary adrenal insufficiency. Plasma renin activity, FT4, TSH, random GH, LH, FSH, and testosterone levels were all within the reference ranges for the second day of life.

The results of the endocrine workup suggested the diagnosis of IAD.

Immediately after diagnosis, at our initiative, we requested data from the peripheral center in which the second sibling had been hospitalized at the age of 7 weeks regarding his endocrine workup. Their records showed that cortisol was first measured 1 day before the child died, during a hypoglycemic episode of 34 mg/dL, and was listed at 0. These results were obtained only after the child died. Therefore, the ACTH level was not measured; these findings did not appear in the discharge papers, and the parents were not notified.

Because IAD is a presumed autosomal recessive disorder, we conducted a molecular analysis of the *TPIT* gene. The findings revealed that the child was homozygous and both parents were heterozygous for a new mutation (IVS4+1G>A) that affects the first nucleotide (G \rightarrow A) of the splice site at the 5' end of the fourth intron (Fig 1).

The patient was treated with a stress dose of hydrocortisone on day 2 of life, which was tapered to a maintenance dose of 15 mg/m². He is currently being treated with 2.5 mg of hydrocortisone with stress increments to 10 mg 3 times daily. At the time of this writing, the child

TABLE 1 Hormonal Levels Measured From Day 2 to Day 8 of Life

Hormone	Day 2	Day 8	Reference Range for Age
Basal cortisol, nmol/L	<27.6		138–690
Stimulated ^a	58		>540
17OHP, nmol/L	3.5		6–28
Stimulated ^a	8.1		<90
ACTH, pmol/L	<2.2	<2.2	2–11.5
TSH, $\mu\text{IU}/\text{mL}$	27.9	1.5	<10
FT4, pmol/L	25	20.7	10.5–25.7
Plasma renin activity, ng/mL per hour	39.5	9.88	<44 (day 2); <26 (day 8)
LH, mIU/mL	7.1		3–8
FSH, mIU/mL	1.72		2–12
GH, ng/mL	7.2		>5
Testosterone, nmol/L	5.0		3–10

^a Sixty minutes post–62.5- μg ACTH stimulation.

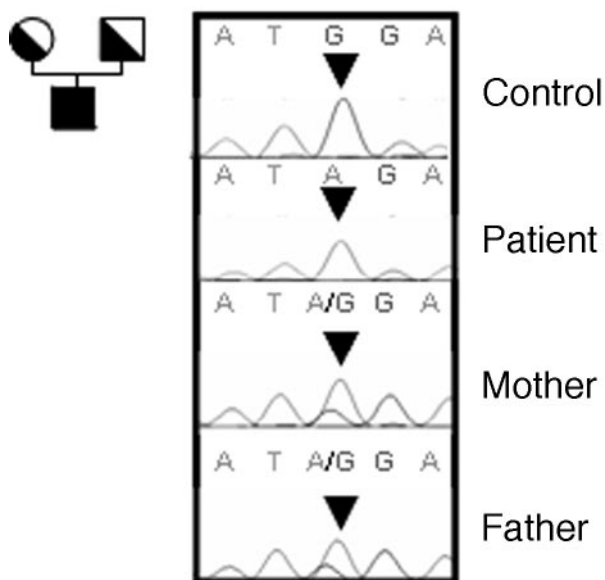


FIGURE 1
DNA sequence and pedigree of the patient carrying the *TPIT* gene mutation IVS4+1G>A. This new *TPIT* gene mutation affects the first nucleotide of the donor splice site of the fourth intron. The black arrowhead indicates the mutant nucleotide as revealed by DNA sequencing.

was 7 months old and had reached all the normal developmental milestones for his age.

DISCUSSION

The most commonly performed tests for prenatal genetic diagnosis are chorionic villus sampling and amniocentesis. Because of the significant risk of spontaneous fetal loss related to these invasive procedures, serum analyte testing has become an important, noninvasive first step in detecting patients who are at risk for congenital abnormalities.⁴ The main purpose of the maternal screening tests is to detect prenatally major malformations such as neural-tube defects or trisomy syndromes, which are either lethal or associated with severe cognitive or physical handicap.⁷

An isolated low estriol level, detected by the triple-marker test, is usually correlated with compromised uteroplacental perfusion and frequently associated with fetal death.⁸ After ruling these out by ultrasound examination, a search for other etiologies should be conducted. The most common genetic cause of extremely low estriol levels is steroid sulfatase deficiency, the prenatal manifestation of X-linked recessive ichthyosis, which affects ~1 in 3000 males.⁹ Other rare causes of low maternal estriol include Smith-Lemli-Opitz syndrome, which is manifested by multiple congenital anomalies, microcephaly, and intrauterine growth retardation, which affects ~1 in 15 000 to 20 000 and is caused by a defect in the final step of cholesterol biosynthesis caused by mutations in the gene encoding 7-dehydrocholesterol reductase.¹⁰ These 2 conditions were

ruled out by test results showing a normal level of steroid sulfatase activity in amniotic cell culture and a normal amniotic-fluid 7-dehydrocholesterol level, respectively.

The absence of maternal virilization during pregnancy, as in our case, makes the diagnosis of placental aromatase deficiency unlikely.¹¹ However, primary¹² or secondary^{3,13} adrenal insufficiency should be suspected. In normal human pregnancy, estriol is produced in a series of steps that involve fetal adrenal, fetal liver, and placental enzymes and is derived almost exclusively from the placental aromatization of the fetal adrenal steroid DHEAS.¹⁴ Anomalies of nature in humans such as anencephaly indicate that ACTH secreted from the fetal pituitary is the principal trophic regulator of the fetal adrenal cortex from approximately the seventh week of gestation.⁵ Therefore, low estriol levels in the context of normal fetal sonography and growth, after exclusion of placental sulfatase deficiency and Smith-Lemli-Opitz syndrome, should raise the suspicion of deficient fetal steroidogenesis, which leads to decreased production of adrenal DHEAS. Fetal adrenal insufficiency can be caused by a mutation in the gene encoding the steroidogenic acute regulatory protein (StAR), which facilitates the transport of cholesterol into the mitochondria and results in lipid adrenal hypoplasia¹⁵ or 17 α -hydroxylase deficiency.¹⁶ However, these entities are associated with XY gender reversal. Thus, the normal male genitalia seen on sonography in our case ruled out these conditions. Other enzymatic defects causing congenital adrenal hyperplasia are associated with elevated fetal DHEAS levels, and therefore estriol levels are not decreased. X-linked congenital adrenal hypoplasia,^{12,17} resistance to ACTH, and secondary adrenal insufficiency,¹³ either isolated or as part of multiple pituitary hormone deficiency, are other possibilities.

Reports of low estriol levels in pregnancies of neonates born with IAD^{2,3,13} or adrenal hypoplasia¹² are scarce. This might be because of the rarity of these syndromes or physician unawareness of the association of low estriol levels with primary or secondary adrenal insufficiency, which was the case with the deceased older brother of the propositus.

Prompt ACTH testing conducted on the second day of life of the younger child enabled early diagnosis of severe cortisol deficiency and immediate initiation of glucocorticoid-replacement therapy. Undetectable ACTH levels suggested the diagnosis of secondary adrenal insufficiency. IAD in the neonatal period is usually associated with the sporadic occurrence of combined anterior pituitary deficiency,^{13,18} including GH, gonadotropins, and thyroid hormones; however, the levels of these were normal. In addition, the parents' consanguinity and the likelihood that the older sibling had IAD suggested an autosomal recessive disorder. Recently, Pulichino et al⁶ and Vallette-Kasic et al¹ published their

findings on autosomal recessive isolated IAD secondary to homozygous or compound heterozygous mutations in the *TPIT* gene.

TPIT is a cell-restricted T-box transcription factor that is important for the terminal differentiation of pituitary pro-opiomelanocortin-expressing cells.^{19,20} In contrast to a mutation in transcription factors involved in early events of pituitary organogenesis, such as Pit-1 or Prop-1 (which cause different combinations of combined pituitary hormone deficiency),¹⁸ loss-of-function mutations in the human *TPIT* gene were detected in autosomal recessive IAD.^{1,6,19,20} These mutations apparently indicate an IAD at the pituitary rather than the hypothalamic level. In patients whose IAD was caused by *TPIT* mutations, the condition had a neonatal onset that presented most frequently with neonatal hypoglycemia or prolonged neonatal cholestatic jaundice.^{1,6} Both ACTH and cortisol levels were extremely low while other pituitary functions were normal. Their symptoms resolved with glucocorticoid therapy. The syndrome was not associated with pigmentation defects or obesity as described in patients with *POMC* gene mutations.²¹ Most importantly, ~25% of those in the series described by Vallette-Kasic et al,¹ which included 21 families, suffered neonatal death without accurate diagnosis, as was the case for our family. As a result, they suggested that IAD might be an underestimated cause of neonatal death.

Our work identified a new intronic *TPIT* gene mutation. This IVS4+1G>A splice-site mutation affects the splice donor site (usually GT) in the fourth intron of the gene. According to the splice database (Genome Browser [www.genome.ucsc.edu]), 98.7% of known expressed sequence tags contain the canonical GT-AG intronic junctions, and 0.56% have noncanonical GC-AG splice-site pairs.²² In the case of our patient, the G → A substitution in the splice-donor site results in an abnormal splice junction (AT-AG) that is incompatible with mRNA splicing. This causes the inclusion of intron 4, resulting in an mRNA with a stop codon 4 base pairs after the 3' end of exon 4. This stop codon probably leads to loss of *TPIT* function by nonsense-mediated mRNA decay, as it does for other *TPIT* nonsense mutations.^{1,7}

Our observation of low estriol levels during pregnancy as a predictor of this condition suggests that each case of low estriol detected by the triple-marker test, after ruling out the common etiologies, should be referred for additional evaluation to a multidisciplinary team that includes a geneticist and pediatric endocrinologist. Prompt ACTH testing in the first neonatal days will allow early diagnosis and immediate institution of therapy, thus preventing unnecessary neonatal death secondary to easily treatable disease.

ACKNOWLEDGMENTS

This study was conducted in Petah Tiqwa, Israel, and Montreal, Canada. Work in Dr Drouin's laboratory is

supported by the National Cancer Institute of Canada and by the Canadian Institutes of Health Research.

We are grateful for the technical assistance of Noa Gur Arie; the laboratory assistance of Drs Yafa Klipper-Aurbach, Eric Erman, and Edna Halabe; and for the editorial assistance of Dr G. Halpern.

REFERENCES

1. Vallette-Kasic S, Brue T, Pulichino AM, et al. Congenital isolated adrenocorticotropin deficiency: an underestimated cause of neonatal death, explained by *TPIT* gene mutations. *J Clin Endocrinol Metab*. 2005;90:1323-1331
2. Zachmann M, Girard J, Duc G, Illig R, Prader A. Low urinary estriol during pregnancy caused by isolated fetal ACTH-deficiency. *Acta Paediatr Scand Suppl*. 1979;277:26-31
3. Malpuech G, Vanlieferinghen P, Dechelotte P, Gaulme J, Labbé A, Guiot F. Isolated familial adrenocorticotropin deficiency: prenatal diagnosis by maternal plasma estriol assay. *Am J Med Genet*. 1988;29:125-130
4. Graves JC, Miller KE. Maternal serum triple analyte screening in pregnancy. *Am Fam Physician*. 2002;65:915-920
5. Mesiano S, Jaffe RB. Developmental and functional biology of the primate fetal adrenal cortex. *Endocr Rev*. 1997;18:378-403
6. Pulichino AM, Vallette-Kasic S, Couture C, et al. Human and mouse *TPIT* gene mutations cause early onset pituitary ACTH deficiency. *Genes Dev*. 2003;17:711-716
7. McDuffie RS Jr, Haverkamp AD, Stark CF, Haverkamp C, Barth CK. Prenatal screening using maternal serum alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol: two-year experience in a health maintenance organization. *J Matern Fetal Med*. 1996;5:70-73
8. Schleifer RA, Bradley LA, Richards DS, Ponting NR. Pregnancy outcome for women with very low levels of maternal serum unconjugated estriol on second-trimester screening. *Am J Obstet Gynecol*. 1995;173:1152-1156
9. Bartels I, Caesar J, Sancken U. Prenatal detection of X-linked ichthyosis by maternal serum screening for Down syndrome. *Prenat Diagn*. 1994;14:227-229
10. Opitz JM, Gilbert-Barness E, Ackerman J, Lowichik A. Cholesterol and development: the RSH ("Smith-Lemli-Opitz") syndrome and related conditions. *Pediatr Pathol Mol Med*. 2002;21:153-181
11. Grumbach MM, Auchus RJ. Estrogen: consequences and implications of human mutations in synthesis and action. *J Clin Endocrinol Metab*. 1999;84:4677-4694
12. Hensleigh PA, Moore WV, Wilson K, Tulchinsky D. Congenital X-linked adrenal hypoplasia. *Obstet Gynecol*. 1978;52:228-232
13. Marshall I, Ugrasbul F, Manginello F, et al. Congenital hypopituitarism as a cause of undetectable estriol levels in the maternal triple-marker screen. *J Clin Endocrinol Metab*. 2003;88:4144-4148
14. Buster J, Carson S. Endocrinology and diagnosis of pregnancy. In: Gabbe S, Niebyl J, Simpson J, eds. *Obstetrics: Normal and Problem Pregnancies*. Philadelphia, PA: Churchill Livingstone; 2002:3-36
15. Stocco DM. Clinical disorders associated with abnormal cholesterol transport: mutations in the steroidogenic acute regulatory protein. *Mol Cell Endocrinol*. 2002;191:19-25
16. Auchus R. The genetics, pathophysiology, and management of human deficiencies of P450c17. *Endocrinol Metab Clin North Am*. 2001;30:101-119
17. Reutens A, Achermann J, Ito M, et al. Clinical and functional effects of mutations in the *DAX-1* gene in patients with adrenal

- hypoplasia congenita. *J Clin Endocrinol Metab.* 1999;84:504–511
18. Cohen LE, Radovick S. Molecular basis of combined pituitary hormone deficiencies. *Endocr Rev.* 2002;23:431–442
 19. Lamolet B, Pulichino AM, Lamonerie T, et al. Pituitary cell-restricted T box factor, Tpit, activates POMC transcription in cooperation with Pitx homeoproteins. *Cell.* 2001;104:849–859
 20. Pulichino AM, Vallette-Kasic S, Tsai JPY, Gauthier Y, Drouin J. Tpit determines alternate fates during pituitary cell differentiation. *Genes Dev.* 2003;17:738–747
 21. Krude H, Gruters A. Implications of proopiomelanocortin (POMC) mutations in humans: the POMC deficiency syndrome. *Trends Endocrinol Metab.* 2000;11:15–22
 22. Burset M, Seledtsov IA, Solovyev VV. SpliceDB: database of canonical and non-canonical mammalian splice sites. *Nucleic Acids Res.* 2001;29:255–259

Low Estriol Levels in the Maternal Triple-Marker Screen as a Predictor of Isolated Adrenocorticotrophic Hormone Deficiency Caused by a New Mutation in the TPIT Gene

Naomi Weintrob, Jacques Drouin, Sophie Vallette-Kasic, Ellen Taub, Daphna Marom, Yael Lebenthal, Gil Klinger, Efrat Bron-Harlev and Mordechai Shohat
Pediatrics 2006;117;322-327; originally published online Jan 3, 2006;
DOI: 10.1542/peds.2005-1973

This information is current as of February 22, 2006

Updated Information & Services	including high-resolution figures, can be found at: http://www.pediatrics.org/cgi/content/full/117/2/e322
References	This article cites 21 articles, 10 of which you can access for free at: http://www.pediatrics.org/cgi/content/full/117/2/e322#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Endocrinology http://www.pediatrics.org/cgi/collection/endocrinology
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.pediatrics.org/misc/Permissions.shtml
Reprints	Information about ordering reprints can be found online: http://www.pediatrics.org/misc/reprints.shtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

