Newborn Screening for Congenital Adrenal Hyperplasia (CAH) was first made possible in 1977 by a test developed using a heel stick capillary blood sample specimen impregnated on filter paper. The feasibility of rapid newborn screening of 21-hydroxylase deficiency (21-OH def) CAH, the predominant form of the disorder, has long been established. The benefits of neonatal screening for CAH have become evident, as described in both past and recent reports, and laboratory assay techniques and diagnostic criteria are continuously being reviewed and modified for increased accuracy and cost-effective application to mass screening of newborns for CAH.

This article serves as an update on the current status of neonatal screening for 21-OH def CAH, as well as a brief overview of the pathophysiology and clinical manifestations of the disorder that underscore the importance of newborn screening for CAH.

PATHOPHYSIOLOGY OF CAH

The adrenal cortex produces life-essential cortisol and aldosterone. It also secretes insignificant amounts of precursor androgens until puberty (Figure 1, page 518). CAH is a family of inherited adrenal cortical disorders that impair steroidogenic enzyme activity essential for cortisol biosynthesis. More than 90% of all CAH cases are caused by 21-OH def. This disorder causes cortisol deficiency with or without aldosterone deficiency. Cortisol deficiency from early fetal life leads to increased adrenocorticotropic hormone (ACTH) secretion through a negative feedback mechanism.

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Adrenal Hyperplasia

salt wasting
This then stimulates excess secretion of the precursor steroids progesterone and 17-OH-progesterone (17-OHP) proximal to the defective 21-hydroxylase step (Figure 1). The precursor steroids can only be metabolized via the androgen biosynthetic pathway, resulting in excess androgen production that leads to virilization in utero and postnatally.

Aldosterone deficiency causes salt wasting (SW). Serum 17-OHP and androstenedione levels in classic 21-OH def CAH are highly elevated, regardless of age and sex. The excretion of urinary pregnanetriol, the metabolite of 17-OHP, and 17-ketosteroids, the metabolites of adrenal androgens, are also increased in all classic patients, but urinary pregnanetriol may not increase in newborns.

The clinical spectrum ranges from classic severe SW form to classic less severe non-SW, also known as simple virilizing (SV) form, and mild non-classic form. Neonates with the most severe form exhibit SW adrenal crisis during the first few weeks of life, peaking at about 3 weeks, manifested by poor feeding, vomiting, loose stools or diarrhea, weak cry, failure to thrive, dehydration, and lethargy. The symptoms of adrenal crisis may not be evident until serum sodium levels are well below 125 mEq/L (Pang, unpublished data, YEAR). If untreated, circulatory collapse, shock, and death are inevitable.

The SW infant mortality rate without newborn screening in Eastern Europe is 11.9%, which is fivefold higher than that of the general population, at 2.29%. Lower cognitive scores, learning disabilities, and permanent brain injury due to shock are observed in some SW children. Affected female neonates have ambiguous genitalia (AG) but have normal internal reproductive anatomy. AG serves as a prompt for clinical diagnosis in many affected infants. Affected males have no physical stigmata of CAH. Without family history, all male neonates and a minority of female neonates are undiagnosed until adrenal crisis.

According to newborn screening data, the SW form affects approximately 70% of CAH patients. Postnatal virilization for girls, precocious pseudo- or true-puberty for boys, and accelerated skeletal maturation for both genders, all of which lead to early growth cessation, occur if inadequately treated. Patients with a less severe classic SV
form of CAH retain partial secretion of cortisol and aldosterone and do not manifest adrenal insufficiency symptoms unless subjected to severe stress, but do exhibit virilization.\textsuperscript{12-17} These females have virilized genitalia similar to SW females. The SV males and some SV females are not diagnosed until much later when obvious symptoms of virilization occur, such as precocious pseudo-puberty or growth acceleration.\textsuperscript{12-17} The markedly advanced skeletal age of SV patients upon late diagnosis contributes to their short adult stature. Late discovery of incorrect male sex assignment in SW and SV females causes extreme emotional distress to the family and matured patients.

Mild 21-OH def is asymptomatic at birth, without virilization. Premature pubescent hair, acne, and mild growth acceleration during childhood are the early symptoms. Pubertal or post-pubertal onset hirsutism, excessive acne, menstrual disorder, and eventual infertility are the late-onset symptoms.\textsuperscript{15,16}

**GENETIC BASIS**

A deleteriously mutated autosomal recessive CYP21 gene transmits 21-OH def. The loci of the two 21-OH genes, including active CYP21 gene and the inactive pseudo CYP21P gene, are in the HLA complex in tandem with C4A and B and TNXA and B genes on chromosome 6P21.\textsuperscript{3,15,16} The CYP21P gene contains many evolutionary and non-functioning deleterious mutations.\textsuperscript{16} These two 21-OH genes are 98% homologous, necessitating expertise in genotyping. The majority of deleterious mutations in the active CYP21 gene are the pseudogene sequences, suggesting a pseudogene sequence transfer through a gene conversion process or a recombination between CYP21 and CYP21P genes.\textsuperscript{15,16} The CYP21 mutant genotypes found in patients from five different CAH populations correlated well with the clinical phenotype of 21-OH def in about 90% of patients, but did not correlate in the remaining patients.\textsuperscript{15}

SW alleles had seriously deleterious genotypes, including large gene deletion/conversion (32%), splicing defect (56%), frameshift, premature stop codon, and single/triple missense mutation. SV alleles had a less deleterious missense mutation (1172N; 35%) or splicing defect (27%).\textsuperscript{15,16} Almost all non-classic alleles had a mildly deleterious missense mutation.\textsuperscript{15,16}

**NEWBORN SCREENING PROCEDURES**

Newborn screening for CAH is performed by measuring 17-OHP concentration in blood spotted on filter paper.\textsuperscript{14} When the dried blood spot is kept at room temperature for at least a month, the 17-OHP remains stable. It remains stable indefinitely when the blood spot is frozen.\textsuperscript{1} Newborn screening for CAH requires a rapid and accurate screening process to prompt the diagnosis of CAH before the onset of SW symptoms. This requires a screening sample collection at 2 to 3 days, plus efficient transport and analytical process. Sampling conducted at less than 1 day has a high false positivity, and sampling beyond the age of 5 to 7 days reduces screening benefit.

Levels of 17-OHP are normally high in premature neonates.\textsuperscript{2-14} Therefore, to yield low rates of false positives and negatives, it is essential to use well-established reference levels of 17-OHP, determined according to birth weight or gestational age, in the blood spots of pre-term and full-term unaffected newborns, as well as affected neonates, if possible. Rapid and clear communication of suspected CAH results to the appropriate health care personnel and family members for prompt diagnostic confirmation, as well as feedback to the screening program about true or false positive cases and false negative cases, are also essential for effective modification of the screening reference values.

The concurrent screening test for other disorders influences the age at which CAH screening samples are collected. In the United States, all programs perform a single sample test for CAH, followed by a second sample test for presumed positive cases.\textsuperscript{4,10,11} The exception is Texas, which conducts two sample tests routinely by obtaining the second sample when the infant is 1 to 2 weeks old.\textsuperscript{12} The first screening samples were collected at the average age of 2.8 days, with means ranging between the ages of 1.5 to 7 days, and were based on 15 US newborn screening programs initiated before 1995.\textsuperscript{19} The sample transport and assay analysis were the most time-consuming processes. The average age in the programs when results were available was 7.6 days, with means ranging from 3 to 18 days.\textsuperscript{19}

**LABORATORY SCREENING ASSAYS**

Three principal assays, including DELFIA, ELISA, and RIA with a commercial kit, are used to measure 17-OHP concentrations in the eluates of single or duplicate 3-mm disc filter paper blood spots without extraction and purification.\textsuperscript{1-14} Samples of the upper 1% to 3% of 17-OHP values in the assays are re-tested for accuracy. If the level is greater than that of presumed positives, a report is sent to the appropriate health center, pediatrician, and pediatric endocrinologist in the area for follow up.\textsuperscript{3,14}

Screening 17-OHP assays are generally non-specific and cannot be compared to diagnostic serum levels assayed following steroid extraction or purification.\textsuperscript{5-14} The screening 17-OHP cut-off level for presumed positives or recall cases have been established in most programs using the results of pilot testing, and by further adjustments based on the results of false positive and negative experiences.\textsuperscript{3-14}
Newborn Screening 17-OHP Levels

<table>
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<tr>
<th>Urgent Levels</th>
<th>Suspected Levels</th>
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<tr>
<td>Full-term: &gt; ___ ng/mL blood</td>
<td>Full-term: &gt; ___ ng/mL blood</td>
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<td>Pre-term: &gt; ___ ng/mL blood</td>
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<th>Ambiguous genitalia newborns</th>
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Stat electrolytes,
Stat serum 17-OHP,
Assessment for treatment in hospital

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<th>electrolytes, serum 17-OHP</th>
<th>2nd filter paper screening or serum 17-OHP test</th>
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Figure 2. General guideline of action for newborns with elevated newborn screening filter paper spot 17-hydroxypregesterone (17-OHP) levels. Specific levels are left blank because each screening program establishes its own cut-offs.

The recall rate for CAH in established US programs is 0.5% to 1%.1-14 Cut-off levels for presumed positive cases, at ages of more than 12 hours to less than 10 days, were variable. The median and range of blood for full-term cases were 43 ng/mL and 35 to 90 ng/mL, respectively, and 90 ng/mL and 45 to 130 ng/mL, respectively, for pre-term infants.19 Affected neonates had screening 17-OHP levels between 35 and 900 ng/mL.13 Such differences in screened 17-OHP values for both cut-off levels and affected neonatal levels are partly due to the use of different reagents, the assay methodology, varying filter paper matrix, and the patient’s disease spectrum.

Tandem mass spectrometry (MS/MS) is not used as a routine screening test for CAH but has the advantage of rapid 17-OHP detection as low as 20 ng/mL in the dried blood spot, as well as detection of 17-OHP levels greater than 90 ng/mL in the blood spots of CAH children.20 MS/MS may eliminate the problems of the variable 17-OHP cut-off levels influenced by different reagents and assay methods, but it will not eliminate paper matrix variability. Comparative study of screening for CAH using MS/MS versus conventional immunoassays is necessary to analyze this method’s cost, speed, accuracy, and reliability. MS/MS may be best used as a complementary test.

Newborn screening programs do not use 21-OH genotyping. This testing requires expertise and is not necessary for diagnosis. It may be helpful in uncertain cases and may aid in genetic counseling.21 However, screening the eight to 10 most common mutations makes this test costly.

RELIABILITY OF SCREENING TESTS

The true to false-positive ratios of CAH screening were 1:24 in North America, 1:47 in Europe, and 1:79 in Japan. Almost all SW neonates were detected with the first sample-screening test.19 Newborn screening for CAH is not intended to detect mild cases, although some are detected with the first screening test. Second sample testing at 1 to 2 weeks of age increased detection of SV, as well as the mild form, in Texas.13 Despite the gestational/sample age-adjusted 17-OHP cut-off levels, premature birth, low birth weight, and samples obtained at less than 1 day of age are the major factors for false positive results.3-14 An international study also showed 10% of neonates, most of whom had the SV form, were missed in newborn screening due to human error, prenatal dexamethasone therapy, and higher 17-OHP cut-off levels for SV CAH.19

EVALUATION OF NEONATES WITH POSITIVE SCREENING RESULTS

In almost all screening programs, two-tier 17-OHP cut-off levels have been established to guide evaluation in full-term and pre-term newborns, using exceptionally elevated urgent levels and moderately elevated suspected levels (Figure 2). Pediatricians should become familiar with these urgent and suspected levels of their local newborn screening program for CAH. Most CAH newborn screening programs report presumed positive results with instructions. Immediate medical evaluation is necessary (eg, serum electrolytes, 17-OHP, and assessment for need of CAH treatment) in newborns with AG, in sick or asymptomatic male newborns with urgent and suspected levels, and in sick females with urgent levels.15 Although this evaluation for CAH is necessary in clinically asymptomatic female newborns with normal genitalia and urgent levels, as well as in sick females with normal genitalia and suspected levels, these newborns are at low risk for SW crisis.15 Normal female newborns with suspected levels are not at risk for SW but should be given at least a second screening test or evaluation to rule out mild CAH.15

Diagnostic serum 17-OHP levels in affected neonates with positive screening results ranged from 10 to 180 ng/mL in SW and from 4 to 100 ng/mL in non-SW forms.2-14 Reported normal serum 17-OHP levels in unaffected full-term neonates are 0.2 to 3.5 ng/mL, with the exception of a few neonates with levels up to 5 ng/mL. Reported normal serum 17-OHP levels in pre-term neonates are 0.2 to 8 ng/mL, with the exception of a few neonates with levels up to 18 ng/mL.4

With age, serum 17-OHP levels decline in unaffected neonates but rise in classic CAH infants.2 Serum 17-OHP lev-
els in SW neonates are generally higher (30 to 1,000 ng/mL) than that of SV neonates (20 to 100 ng/mL), although the values overlap widely between the two forms. Neonates with the mild form exhibit lower 17-OHP levels (1.5 to 50 ng/mL) than SW and SV patients. In infants, especially pre-terms, with mildly elevated 17-OHP levels of 4 to 10 ng/mL, the ACTH-stimulation test helps rule out mild non-classic 21-OH def.

SW diagnosis requires evidence of hyponatremia and hyperkalemia or increased urinary sodium excretion, persistently elevated renin levels, or both. In asymptomatic infants, serial evaluation of electrolytes throughout the neonatal period is also necessary if they remain normal. CYP21 genotyping serves as an adjunct test to confirm the diagnosis in uncertain cases and helps predict the phenotype in most cases.

NEONATAL INCIDENCE

In the past 2 decades, more than 17 million neonates were screened for CAH worldwide. Health organizations in 13 countries, including 34 states in the United States, perform or will soon perform newborn screening for CAH.

The incidence of CAH in the general population, as shown by newborn screening, ranges from as high as one in 5,000 live births in Saudi Arabia to as low as one in 21,270 live births in New Zealand. The newborn screening incidence in the US and Canada is one in 14,203 live births, which is higher than a 1958 to 1981 case-survey incidence of one in 27,000. Europe’s newborn screening incidence of one in 1,863 live births was also higher than its survey-based incidence of one in 15,000 live births.

The only South American program, in Brazil, has a newborn screening frequency of one in 10,190 live births. Japan’s CAH newborn screening incidence of 1 in 18,827 live births is higher than its survey incidence of one in 43,764. An exceedingly high frequency of CAH exists among Yupik Eskimos from western Alaska, at one in 282 live births by newborn screening. A high incidence of CAH of one in 6,071 live births was also reported on the French island of LaReunion.

BENEFITS OF NEWBORN SCREENING

The goals of newborn screening are to prevent life-threatening adrenal crisis, thereby averting shock, its sequela (ie, brain damage), and death; to prevent male sex assignment of virilized female newborns; and to prevent progressive effects of excess adrenal androgens, which ultimately cause short stature, gender confusion in girls, and psychosexual disturbances in boys and girls. Serum sodium level at diagnosis of SW CAH with newborn screening (mean sodium of 135 mEq/L) and without newborn screening (mean sodium of 125 mEq/L) demonstrated the prevention of severe SW by newborn screening.

Worldwide newborn screening data show screening prompted early diagnosis of CAH before clinical suspicion in 67% of affected newborns, including many females with AG. The remaining affected infants with positive screening results were clinically suspected due to AG (30%), family history, or SW symptoms. The mortality rate from CAH after newborn screening is not yet established. Other benefits of newborn screening include improved case detection evidenced by higher incidence versus that of case-survey reports, improved detection of SW patients (70% by newborn screening versus 43% to 60% of pre-newborn screening), and improved detection of males evidenced by equal sex ratio compared to the pre-newborn screening ratio of .6 males to one female.

PROBLEMS WITH SCREENING

Two major problems inherent in the newborn screening process are the cost and psychological impact of evaluating
false positive cases.2-14,19 Ongoing refinement of the gestational age-adjusted reference levels of 17-OHP in both unaffected and affected neonates is needed to reduce both false positive and false negative results. The cost of detecting one CAH case by a single sample test was $70,000 to $115,000 in Texas, excluding the cost of false positive evaluation.24 The cost of analysis in other programs is being studied.

Educational needs are another concern. All health professionals involved with newborn screening for CAH need to be informed about CAH background information, the importance of rapid screening and immediate evaluation of neonates with positive CAH screening results, the need for medical evaluation for symptomatic patients (i.e., AG, SW, virilization, growth acceleration, premature pubarche) even if the CAH screening test is negative, and the fact that newborn screening for CAH is not aimed to screen for, but may detect some, mild forms of CAH or other rare causes of CAH.

TREATMENT OF CAH

Medical treatment for CAH involves the replacement of inadequately produced cortisol, which suppresses increased ACTH, 17-OHP, and androgen secretion for all symptomatic forms, as well as replacement of deficient aldosterone with an analog of mineralocorticoid (Florinef) for SW patients.15,16 Adequate medical therapy restores normal energy, glucose, electrolytes, fluid balance, and sense of well-being. It also prevents excess adrenal androgen effects. Special medical care is needed in cases of stress. In virilized female infants, surgical intervention is generally performed prior to 1 year and, if necessary, performed again before menarche.

Classic CAH adults do not always reach their genetic potential for height.16 Obesity is also prevalent with standard glucocorticoid therapy (Pang, unpublished data, YEAR). Inadequate medical therapy is associated with male and female infertility.15,16 Experimental antiandrogenic and anti-estrogenic drug therapy to improve height outcome is ongoing for CAH children,25 and other experimental pharmacological therapies are under consideration. Adrenalectomy is recommended only in cases where medical therapy is ineffective.16 The mortality rate in treated patients has been reported to be 4.6%.26 Information on CAH patients’ quality of life as adults is limited, but in one report, many stated they had a favorable outcome.26

PRE-NATAL DIAGNOSIS AND TREATMENT

First trimester diagnosis is made by chorionic villus biopsy sampling after a fetal age of 9 weeks for CYP21 gene analysis.15,16 First trimester diagnosis is limited to mothers receiving prenatal dexamethasone therapy for a fetus at risk of CAH.15,16 Second trimester diagnosis is made after a fetal age of 14 weeks by amniotic fluid sampling.15 Elevated amniotic 17-OHP levels (greater than 6 to 18 ng/mL) shown by a specific assay are diagnostic, but normal levels do not exclude SV or non-classic forms.27 The level may not be elevated in mothers receiving dexamethasone therapy. CYP21 genotyping of chorionic villus cells or amniocytes, probands, and parents’ leukocytes are performed by various PCR or hybridization techniques.15,16

Prenatal treatment is recommended only for female fetuses with classic virilizing CAH. Maternal dexamethasone therapy at 20 mcg per kilogram of her weight per day, beginning around fetal age of 5 to 8 weeks, prevents or reduces AG in most affected females.15,16,22 Prenatal dexamethasone therapy for CAH is controversial because treatment must begin blindly, before either fetal sex or CAH diagnosis can be made, and
because seven-eighths of fetuses are subject-
ected to this therapy unnecessarily. Also, the long-term safety of early exposure to
dexamethasone in utero is unproven to date. Maternal side effects include
cushingoid features of excessive weight gain, intense striae, edema, discomfort,
and emotional instability. Recently, the Lawson Wilkins Pediatric Endocrine
Society/European Society for Pediatric Endocrinology consensus on pre-
natal CAH therapy recommended that this special-
ized therapy be undertaken by designated teams using a national protocol
approved by the institutional review boards and after informed consent
regarding the risks and benefits of the therapy, and that prospective follow-up
and safety data analysis of prenatally treated children be performed by inde-
pendent committee. 22

GENETIC COUNSELING
Family members of CAH-affected patients should be informed about the
nature of CAH, as well as autosomal recessive inheritance. Phenotypically
normal parents should be included, because obligate carriers (unless proven
to be patients) have a 25% chance of having affected offspring. Obligate carriers
also have a 50% chance of having carriers and a 25% chance of having non-carrier-
unaffected offspring or siblings. Family members should be aware of the availability of
CYP21 DNA testing for carrier and prenatal diagnosis, and the indications, benefits, known risks, and
lack of long-term safety data of prenatal
dexamethasone therapy.

Carrier testing includes CYP21 geno-
typing, which is a more precise test than
ACTH-stimulated serum 17-OHP levels
that overlap between non-carrier and car-
rriers for CAH. 15,16 Genotyping is limited to
the proband, if known. If the proband is
absent, genotyping of the eight to 10
most common mutations can be per-
formed by some commercial laboratories.

REFERENCES
1. Pang S, Hotchkiss J, Draha AL, Levine LS,
   New MJ. Microfilter paper method for 17-
   hydroxy-progestrone radioimmunoassay:
   its application for rapid screening for congenital
   adrenal hyperplasia. J Clin Endocrinol Metab.
   1977;45:1003-1008.
   newborn screening program for congenital
   adrenal hyperplasia in Alaska. J Clin Endocrinol
   Metab. 1982;55:413-420.
   wide experience in newborn screening for
   classical congenital adrenal hyperplasia due to
4. Pang S, Clark A. Congenital adrenal hyper-
   plasia due to 21-hydroxylase deficiency:
   Newborn screening and its relationship to the
diagnosis and treatment of the disorder.
   Screening. 1993;2:105-139.
5. Suwa S. Nationwide survey of neonatal mass
   screening for congenital adrenal hyperplasia in
6. Curfield WS, Webster D. Newborn screening
   for congenital adrenal hyperplasia in New
7. Al-Nuaim AA. Newborn screening program
   (NSP) in Saudi Arabia (SA). In: Programs and
   Abstracts of the 3rd International Newborn
   Screening Meeting, Jamaica Plain,
   Mass. New England Regional Newborn
   Screening Program. 1996;89.
8. Balsamo A, Cacciari E, Piazz S, et al. Congen-
   ital adrenal hyperplasia: neonatal mass
   screening compared with clinical diagnosis
   only in the Emilia-Romagna region of Italy,
9. Saedi SA, Dean D, Dent W, Stockel E, Cronin
   C. Screening for congenital adrenal hyperpla-
   sia: the Delfia Screening Test overestimates
   serum 17-hydroxyprogestrone in preterm
    Improved precision of newborn screening for
    congenital adrenal hyperplasia by using weight-
    adjusted criteria for 17-hydroxyprogesterone in
11. Pang S, Shook MK. Current status of neonatal
    screening for congenital adrenal hyperplasia.
    Benefits of neonatal screening for congenital
    adrenal hyperplasia (21-hydroxylase deficio-
13. Terrell BL Jr, Berenbaum SA, Manter-
    Kapanke V, et al. Results of screening 1.9
    million Texas newborns for 21-hydroxylase-
    deficient congenital adrenal hyperplasia.
14. Honour JW, Torresani T. Evaluation of neo-
    natal screening for congenital adrenal hyperpla-

Endocrinol Metab Clinics of N Amer.
1997;26:853-891.
16. White PC, Speiser PW. Congenital Adrenal
    Hyperplasia due to 21-hydroxylase deficien-
    from 30 years of clinical diagnosis and treat-
    ment of congenital adrenal hyperplasia in five
    middle European countries. J Clin Endocrinol
    Metab. 2000;86:2958-2964.
    Presentation, acute illness, and learning diffi-
    culties in salt wasting 21-hydroxylase deficien-
    on Newborn Screening for Congenital Adren-
    al Hyperplasia: Investigation Update on New-
    born Screening for Congenital Adrenal
    Hyperplasia in a Greater Worldwide Popula-
    tion. Paper presented at: International New-
    born Screening Society Meeting; October 21-
    24, 1996; Boston, Mass.
20. Lai CC, Tsai CH, Tsai FJ, et al. Monitoring of
    congenital adrenal hyperplasia by microbore
    HPLC-electrospray ionization tandem mass
    spectrometry of dried blood spots. Clin
21. Nordenstrom A, Thilen A, Hagenfeldt L,
    Larsson A, Wedell A. Genotyping is a valu-
    able diagnostic complement to neonatal
    screening for congenital adrenal hyperplasia
due to steroid 21-hydroxylase deficiency. J
    Clin Endocrinol Metab. 1999;84:1505-1509.
22. Joint LWPES/ESPE CAH Working Group,
    Writing Committee. Consensus Statement on
    21-hydroxylase Deficiency from the Lawson
    Wilkins Pediatric Endocrine Society and the
    European Society for Pediatric Endocrinology.
    J Clin Endocrinol Metab. 2002;87:4048-4053.
23. Van der Kamp HJ, Noordam K, Elvers B, et
    al. Newborn screening for congenital adrenal
    comparative cost analysis of newborn screening
    for classic congenital adrenal hyperplasia in
25. Merke DP, Keil MF, Jones JV, Fields J, Hill S,
    Cutler GB Jr: Flutamide, testolactone, and
    reduced hydrocortisone dose maintain normal
growth velocity and bone maturation despite
    elevated androgen levels in children with con-
    genital adrenal hyperplasia. J Clin Endocrinol
    Metab. 2006;85:1114-1120.
26. Jääskeläinen, Voutilainen R. Long-term out-
    come of classical 21-hydroxylase deficiency:
    diagnosis, complications and quality of life.
    otic fluid concentrations of D5 and D4 steroid in
    fetuses with congenital adrenal hyperplasia due
to 21-hydroxylase deficiency and in anen-
    cephalic fetuses. J Clin Endocrinol Metab.