By Harold N Bass, MD
Jamie Beavers Taylor, BSc

Perinatal Screening for Congenital Malformations and Genetic Disorders: Current Status and Future Directions

Summary

Developed during the past four decades, perinatal screening for congenital malformations and genetic disorders has revolutionized health care for pregnant women and young infants. We review the current status of prenatal and newborn screening, highlight some of KP's contributions to this area of health care, and explore future directions in clinical screening.

Introduction

Perinatal screening for congenital malformations and genetic disorders had its inception four decades ago, when testing of newborns for phenylketonuria began. Today, in part because of pilot studies conducted by the Southern California Permanente Medical Group (SCPMG) and The Permanente Medical Group (TPMG) (see next section), second-trimester prenatal screening for neural tube and abdominal wall defects, Down syndrome, and trisomy 18 is widely done by means of biochemical markers (alpha-fetoprotein, human chorionic gonadotropin, unconjugated estrogen, and inhibin A). Population-based antenatal screening for additional disorders, such as cystic fibrosis, Tay-Sachs disease, and hemoglobinopathies, has also grown in popularity. Current research efforts are directed toward first-trimester screening for Down syndrome and identification of fetal cells within the maternal circulation.

Newborn screening for phenylketonuria, galactosemia, and hypothyroidism is done in all 50 states. Selected states conduct additional screening for biotinidase deficiency, congenital adrenal hyperplasia, cystic fibrosis, hearing loss, homocystinuria, and maple-syrup urine disease, as well as for sickle cell disease and other disorders of hemoglobin production. Screening for amino acidemia, organic acidemia, and fatty acid oxidation disorders by tandem mass spectrometry is under active investigation in California and several other states and is already being utilized for suspected metabolic disorders by SCPMG's Regional Genetic Testing Laboratory.

Prenatal Screening Programs: Current Status of Prenatal Screening for Neural Tube Defects

Prenatal screening began with the discovery by British investigators, in the early 1970s, that open neural tube defects (NTDs)—anencephaly, spina bifida, and encephalocele—were associated with an elevated concentration of alpha-fetoprotein (AFP) in the amniotic fluid and maternal serum.[1] During pregnancy, small amounts of AFP (a glycoprotein with a molecular weight of approximately 70,000 daltons synthesized by the embryonic yolk sac and fetal liver) enters the amniotic fluid via fetal urination, gastrointestinal secretion, and transudation from exposed blood vessels.[2] AFP crosses the placenta and enters the maternal circulation, where it can be measured in the serum.[2] AFP can be detected in maternal serum by seven or eight weeks of gestation and reaches a peak concentration at about 30 weeks of gestation.[2] (Whereas most open NTDs are accompanied by an elevated level of maternal serum AFP, closed NTDs are not associated with abnormal AFP levels.)

Prenatal Screening for Down Syndrome

In 1984, a reduced AFP level in maternal serum was found useful as a screening test for Down syndrome.[3] When combined with two additional second-trimester biochemical markers (serum human chorionic gonadotropin (hCG) and unconjugated estriol) at a 5% false-positive rate, the rate of accurately detecting Down syndrome among women under age 35 years rose from 25% to 60%.[4] Use of a fourth marker, inhibin A, will be added to the California screening program in the next year and will increase the Down syndrome detection rate to 75% among women under age 35 years.[5] Thus, measuring four serum markers (AFP, hCG, unconjugated estriol, and inhibin A) in women younger than 35 years during the second trimester in combination with genetic amniocentesis or chorionic villus sampling (CVS) in women 35 years or older should allow the prenatal detection rate for Down syndrome

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HAROLD N BASS, MD, (top) who is board-certified in Pediatrics and Medical Genetics, has been with the Southern California Medical Group in Panorama City for over 30 years. In addition, Dr Bass is an elected member of the SCPMG Board of Directors, a full clinical professor at the University of California Los Angeles (UCLA) School of Medicine, and an adjunct professor of Biology at California State University, Northridge, where he was instrumental in establishing a graduate program in genetic counseling. Dr Bass is a graduate of the University of Chicago's Pritzker School of Medicine. E-mail: Harold.N.Bass@kp.org.
JAMIE BEAVERS TAYLOR, BSc, (bottom) will be awarded a master's degree in Genetic Counseling by California State University, Northridge, next spring. Ms Taylor received a bachelor's degree in Psychobiology from UCLA in 2000. The work presented here was done while Ms Taylor was on a clinical rotation with Kaiser Permanente's Valley Service Area.

Table 1. Differential diagnosis made on the basis of an elevated level of maternal serum AFP
Conditions of fetal origin:
Abdominal wall defects (gastroschisis, omphalocele)
Congenital nephrosis of Finnish type
Cystic adenomatoid malformation of lung
Cystic hygroma
Decreased maternal weight
Epidermolysis bullosa
Fetal death or impending fetal demise
Fetomaternal hemorrhage
Gastrointestinal obstruction (eg, diaphragmatic hernia, duodenal atresia, esophageal atresia)
Multiple gestation
Oligohydramnios
Open neural tube defects (anencephaly, encephalocele, spina bifida)
Renal agenesis
Sacrococcygeal teratoma
Triploidy
Underestimated fetal age
Urethral obstruction
Conditions in which elevated α-fetoprotein level may occur independent of pregnancy or sex:
Ataxia-telangiectasia
Cirrhosis of liver
Cystic fibrosis
Germ cell tumor
Hepatitis
Hepatoblastoma
Hepatocellular carcinoma
Hereditary tyrosinemia
Yolk sac tumor

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to reach 95% (Table 2). Genetic amniocentesis or CVS is the standard testing recommendation for women older than 35 years, who account for 20% of Down syndrome births.

Prenatal Screening for Other Medical Conditions

An elevated AFP concentration may also occur in other conditions (Table 1), including multiple pregnancy (eg, twin gestation); fetal abdominal wall defects (omphalocele and gastroschisis); Turner syndrome with cystic hygroma; fetal bowel obstruction (esophageal atresia, duodenal atresia, congenital diaphragmatic hernia); cystic adenomatoid malformation of the lung; congenital nephrosis of the Finnish type; epidermolysis bullosa; teratoma; and actual or impending fetal demise.[6]

Population-based prenatal screening programs currently include molecular or enzymatic testing for Tay-Sachs disease in persons of Ashkenazi Jewish, Cajun, or French-Canadian ancestry; use of hemoglobin electrophoresis to detect sickle-cell hemoglobinopathy in persons of African or African-American origin; and determination of mean corpuscular volume (MCV) from a complete blood count among persons with African, Asian, or Mediterranean background. (A decreased MCV in a non-iron-deficient individual may be indicative of alpha- or beta-thalassemia trait.)

Within all Kaiser Permanente (KP) divisions nationwide, prenatal screening is routinely conducted for possible Rh and ABO blood group incompatibility and for certain infectious agents, including hepatitis B, human immunodeficiency virus (HIV), rubella, syphilis, group B streptococcus, and varicella-zoster. A positive finding may have implications for fetal hydrops, neonatal jaundice, transplacental infection, or teratogenicity.

Table 2. Biochemical screening results diagnostic for neural tube defects, Down syndrome, and trisomy 18

	Neural tube defects	Down syndrome[a]	Trisomy 18
α-fetoprotein level	High	Low	Low
Chorionic gonadotropin level	Normal	High	Low
Unconjugated estriol level	Normal	Low	Low
Inhibin A level	Normal	High	Normal

[a]also known as trisomy 21

Reduced levels of the three most widely used serum markers—AFP, hCG, and unconjugated estriol—are associated with an increased risk of trisomy 18.[7] When maternal age was combined with a finding of decreased levels of these three analytes, trisomy 18 was accurately detected at a rate of 60%.[8]

Organized prenatal screening programs (eg, in California and Great Britain) that measure serum AFP concentration and additional biochemical markers have established that the period between 15 and 20 gestational weeks is the optimal time for obtaining a maternal blood sample.

Women in whom an "unexplained" elevated maternal serum AFP level is found after detailed (ie, level II) ultrasound studies and normal results of amniocentesis face an increased risk of second-trimester fetal demise, preterm birth, placental abruption, preeclampsia, and intrauterine growth restriction,[9,10] although a similar risk for adverse perinatal outcome was not shown by TPMG investigators studying a large series of patients with unexplained elevated hCG levels.[11] A very low maternal serum estriol level may be associated with congenital X-linked ichthyosis caused by steroid sulfatase deficiency[12] or with a rare autosomal-recessive disorder of cholesterol metabolism, Smith-Lemli-Opitz syndrome.[13]

Prenatal Screening Using Ultrasonography

Ultrasound has become another screening tool widely used by clinicians who care for pregnant women. Under standards established by the American College of Radiology,[14] the American College of Obstetricians and Gynecologists (ACOG),[15] and the American Institute of Ultrasound in Medicine,[16] current practice is to perform a detailed ultrasound survey of the fetal anatomy and related structures in all prenatal patients at between 18 and 20 weeks of gestation. For most women with an isolated finding of choroid plexus cyst, hyperechogenic bowel, or pyelectasia <4 mm in a fetus with otherwise normal growth parameters, pregnancy outcome is normal. Some may consider these findings "nondisease of high technology"; nonetheless, patients with these findings in addition to a sonographic abnormality (eg, congenital heart defect, oligohydramnios, or suboptimal fetal growth) should receive further intervention or closer follow-up for perinatal complications.

KP's Contribution to Prenatal Screening Programs

After assessing the utility of prenatal screening, two KP entities—SCPMG and TPMG—produced data that ultimately led to passage of legislation requiring that maternal serum AFP screening be provided to all pregnant women in California who choose to receive this service. In 1984, KP's California Division inaugurated screening programs in Northern and Southern California; today, 85% of women within KP receive voluntary second-trimester AFP screening, whereas 75% of women statewide receive this screening (S Goldman, MPH, personal communication, 2001). Another KP screening program—TPMG's population-based prenatal screening program for cystic fibrosis—began in November 1999, and is currently the largest of its kind.

The California Department of Health Services' Genetic Disease Branch contracts with TPMG and SCPMG to conduct state-mandated voluntary perinatal screening for Health Plan members of the KP California Division. As a result, both medical groups have developed a sophisticated infrastructure which, under regional coordination and as the need arises, provides professional and member education, genetic counseling, ultrasound studies, amniocentesis, laboratory services, and clinical follow-up by obstetricians, perinatologists, pediatric endocrinologists, pediatric hematologists, infectious disease specialists, audiologists, or metabolic specialists (geneticists and nutritionists). TPMG also publishes a newsletter for internal distribution ("The Screen"), and both SCPMG and TPMG have developed multidisciplinary clinics for the care of patients with craniofacial malformation, cystic fibrosis, forms of hemoglobinopathy, metabolic disorders, and spina bifida.

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New Directions in Prenatal Screening

Screening methods for improved detection of Down syndrome are being investigated. The most promising of these methods uses pregnancy-associated protein A (PAPP-A) and either hCG or its free beta subunit in maternal serum in combination with sonographic measurement of the nuchal fold at 11 to 14 weeks of gestation.[17] CVS or amniocentesis is used to confirm a positive screening result, which is denoted by a reduced serum PAPP-A level in conjunction with an elevated level of hCG (or its free beta subunit) and increased nuchal fold thickness.[17]

First- or second-trimester gestational screening for Down syndrome may be further enhanced when immunoassay is performed for urinary hyperglycosylated human chorionic gonadotropin (H-hCG—also known as invasive trophoblast antigen, or ITA), a substance which is produced in greatest quantity at the beginning of pregnancy. Problems encoun-

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tered with determination of serum H-hCG levels led investigators to measure urinary H-hCG, in which the median level was found to be 9.5-fold higher in Down syndrome cases.[18] Although further studies of H-hCG are needed, measurement of four second-trimester serum markers (AFP, hCG, unconjugated estriol, and inhibin A) with urinary H-hCG detected 96% of Down syndrome cases (false-positive rate, 5%) in women of advanced maternal age (≥35).[18]

Molecular-based screening for cystic fibrosis (a potentially devastating autosomal-recessive pulmonary and digestive disorder) was the subject of a 1997 National Institutes of Health consensus conference.[19] The American College of Medical Genetics and ACOG recently agreed on a panel of DNA probes for use in prenatal screening for cystic fibrosis.[20] Voluntary preconception or prenatal screening for cystic fibrosis is particularly useful when offered to those with a positive family history of cystic fibrosis and to persons of European or Ashkenazi Jewish background, among whom a carrier frequency of one in 25 to one in 30 is higher than in other population groups. The mutation detection rate among Caucasians is 97% in the Ashkenazi Jewish population and 80% in persons of European background; it is lower in other groups.[20]

Retrieval of fetal cells from maternal blood early in pregnancy is another potential noninvasive screening method for detecting aneuploidy and other antenatally diagnosable conditions if certain technical challenges can be overcome. These challenges include identification of markers unique to fetal cells; determining whether a particular fetal cell type originated in the current pregnancy; and achieving advances in cell-sorting technology for cell enrichment and purification. Investigations are primarily focused on isolation of fetal nucleated red blood cells and trophoblast sprouts, which do not persist in the maternal circulation after the current pregnancy.[21]

Current Status of Newborn Screening

At present, all 50 US states and the District of Columbia conduct universal newborn population screening and follow-up programs for phenylketonuria (PKU), galactosemia, and hypothyroidism. Each of these conditions, if untreated, has cataclysmic consequences for the infant, and all three fulfill well-established criteria for newborn population screening. Successful screening programs target serious, relatively common disorders for which treatment is available; include relatively inexpensive screening tests that are easy to perform; and promptly communicate results (ie, to parents and physicians) as well as institute treatment.[22]

Several US states screen for additional disorders which fulfill these criteria for population screening of newborns. These disorders include forms of sickle-cell hemoglobinopathy and hemoglobin H disease, screening for which is currently done in California; maple-syrup urine disease (MSUD), a disorder of branched-chain amino acids; congenital adrenal hyperplasia (21-hydroxylase deficiency), which, if undetected, may result in addisonian crisis and shock at one or two weeks of age; biotinidase deficiency; and homocystinuria (Table 3).

New Directions in Newborn Screening

Two US states—Colorado and Wisconsin—currently screen neonates for cystic fibrosis using a two-stage approach in which the immunoreactive trypsinogen level is determined from a blood spot. If testing shows elevated trypsinogen level, molecular analysis is done for several common cystic fibrosis mutations, to be followed by confirmatory sweat chloride testing. Early diagnosis and intervention can improve nutritional status in infants and young children with cystic fi-

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Table 3. Status of newborn screening programs in the United States

Conditions screened for nationwide (50 states):
Congenital hypothyroidism
Galactosemia
Phenylketonuria
Hyperphenylalaninemia
Conditions currently screened for in selected states:
Biotinidase deficiency
Congenital adrenal hyperplasia
Cystic fibrosis
Hearing loss
Hemoglobin disorders (eg, sickle cell, alpha-thalassemia)
Homocystinuria
Maple-syrup urine disease
Conditions likely to be subjects of future screening programs using tandem mass spectrometry:
Amino acidemia
Fatty acid oxidation disorders
Organic acidemia

brosis but has only limited effect on pulmonary function.[23] In an ethnically diverse location such as California, newborn screening for cystic fibrosis has a major drawback: current methods do not enable identification of the full range of cystic fibrosis mutations. For example, about 40% of these mutations remain unidentified among the growing number of Hispanic infants born each year in the Golden State.[20]

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Between one in 1000 and one in 3000 infants is born with clinically significant hearing loss.[24] This figure is even higher among babies admitted to neonatal intensive care units.[24] Implementation of noninvasive universal newborn hearing screening—first instituted in Rhode Island—can substantially lower the age at which congenital hearing loss is identified in children.[25] At many testing centers, initial screening is done using evoked otoacoustic emissions (EOAE) to measure sound waves generated by ciliary movement within the cochlea: Miniature microphones placed in the infant's external auditory canal produce clicks or tone bursts to which the cilia respond.[24] Compared with the automated auditory brainstem response (ABR) test, which requires the infant to be in a quiet state, EOAE is easier to do but more frequently yields false-positive results (especially during the first 24 hours of life) as a result of debris in the ear canal or fluid in the middle ear.[24] Tracking and referral to an audiologist for definitive diagnosis is required for infants who fail the ABR test. Referral rates under 4% can usually be achieved when EOAE is combined with the automated ABR test or when the automated ABR test alone is used.[24]

For quantitation of amino acids during newborn screening, tandem mass spectrometry (MS/MS) is more accurate than most current methods and thus detects phenylketonuria, MSUD, and homocystinuria more sensitively and specifically.[26] The screening menu for tandem mass spectrometry can facilitate identification of additional disorders not currently included in screening panels. Among these disorders are medium-chain acyl-CoA dehydrogenase deficiency (a disorder of fatty acid oxidation) and glutaric aciduria type 1 (an organic acid disorder), both of which are relatively common disorders that are difficult to detect before onset of symptoms and whose outcome is improved by early treatment.[26] Other forms of aminoacidopathy, organic acidemia, and disorders of fatty acid metabolism also can be diagnosed early with tandem mass spectrometry.[26] Although many of these inborn errors of metabolism (most of which are inherited as autosomal-recessive traits) are not yet treatable and thus might not fulfill conventional criteria for newborn population screening, early diagnosis can assist parents in planning for future children.[26] The California Department of Health Services' Genetic Disease Branch is conducting a pilot study utilizing MS/MS on newborn screening samples, and SCPMG's genetic testing laboratory recently installed a tandem mass spectrometer to facilitate the diagnosis of suspected metabolic disorders among individuals of all ages.

Conclusions

The future looks promising for perinatal screening. Use of biochemical markers (ie, PAPP-A, hCG, H-hCG) and measurement of the nuchal fold may make first-trimester screening for Down syndrome a desirable option. Addition of inhibin A to the AFP-hCG-unconjugated estriol panel will improve second-trimester detection of Down syndrome and lower the false-positive rate. For persons with a family history of cystic fibrosis and for susceptible populations based on ethnic backgrounds, voluntary screening for cystic fibrosis mutations has proved a valuable prenatal diagnostic tool. Researchers may soon be able to retrieve fetal cells from the maternal circulation to noninvasively conduct prenatal screening for fetal chromosome abnormalities and other identifiable disorders.

Newborn screening for cystic fibrosis has been shown to improve the nutritional status of affected infants and young children, and additional mutations related to cystic fibrosis are being investigated in diverse populations. Implementation of noninvasive, universal hearing screening for newborns is lowering the age at which children with congenital hearing loss are identified. Tandem mass spectrometry for newborn screening is more sensitive and specific than most current screening methods and is capable of detecting a greater variety of inborn errors of metabolism. Although some targeted diseases may not yet be treatable, early intervention can improve the outcome for many children with metabolic disorders and enable parents to obtain timely information about prenatal diagnostic options relevant for future pregnancies. ❖

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