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The U. S. Surgeon General has advised women not to drink if they become pregnant, plan to become pregnant, or are at risk of becoming pregnant. Innocent children suffer the consequences of physical, mental, and behavioral manifestations that can extend into adulthood. Since fetal alcohol syndrome is 100% preventable, the primary care physician needs to be vigilant and diligent in the education of female adolescents and women of childbearing age. This issue highlights the spectrum of fetal alcohol syndrome, its recognition, and treatment.

—The Editor

An Overview of Fetal Alcohol Spectrum Disorders for Physicians

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Introduction

The idea that a fetus could be harmed by exposure to alcohol during pregnancy has been around for a long time. Perhaps the first written record is in the Bible, Judges 13:4, in which the birth of Samson is being discussed. The angel of the Lord appears to Samson's mother and says "Now see to it that you drink no wine or other fermented drink and that you do not eat anything unclean, because you will conceive and give birth to a son." Experimental data regarding the effects of alcohol on a fetus have been conducted since near the beginning of the 20th century with the use of animal models.[1] The first journal article was published in 1968, when Lemoine et al.[2] reported the common problems of 127 children born to mothers who drank large amounts of alcohol during pregnancy. This report was largely ignored until 5 years later, when Jones and Smith in 1973[3] described children of similar symptoms and coined the term "fetal alcohol syndrome." This term was used to describe a group of children, born to alcoholic mothers, who had growth retardation, characteristic facial features, and central nervous system involvement. It is now well known that prenatal alcohol exposure may lead to fetal alcohol spectrum disorders (FASD), an umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy, including fetal alcohol syndrome. Since then, there have been four decades of research on the damaging, and potentially irreversible, effects of prenatal alcohol exposure to the child.

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FASD is widespread within the United States and occurs in any population where women drink alcohol during pregnancy.[4] Consequently, FAS has been identified in all racial and ethnic groups.[5] In addition, FASDs are the most common form of developmental disabilities and birth defects in the western world, more prevalent than Down syndrome and autism.[6] Furthermore, FASD is 100% preventable, since the development of FASD depends primarily on exposure of the fetus to alcohol.

This article addresses FASD with regard to the needs of the primary physician. FASD goes largely under-diagnosed in the United States, and primary care physicians may be unprepared to deal with the ramifications this diagnosis may bring.[7] Children with even full-blown FAS often go undetected at birth and later in life.[8] Children with a less severe form of FASD are even more problematic to diagnose because the physical signs often are more subtle.[9] A review of FASD is necessary in order to provide the primary physician with more knowledge and tools to deal with this significant problem.

Fetal Alcohol Spectrum Disorders

The range of adverse effects of alcohol on human development during pregnancy is termed fetal alcohol spectrum disorders. The term FASD is not a diagnostic term, but rather a term for the broad continuum of effects, ranging from physical, mental, or behavioral effects, that develop in the fetus as a consequence of maternal consumption of alcohol. Often these effects have lifelong implications. There have been a variety of terms previously used to address this issue, including fetal alcohol effects, alcohol-related neurodevelopmental disorders, and alcohol-related birth defects.

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Executive Summary

- Fetal alcohol syndrome is the most common form of developmental disability and birth defect in the Western world.
- Manifestations include physical, mental, and/or behavioral effects commonly associated with growth retardation, facial dysmorphism, and CNS problems.
- Alcohol is a teratogen that affects the CNS. There is no "safe" amount of consumption during pregnancy.
- Despite warning labels on alcoholic containers and recognition of the syndrome for 40 years, alcohol use among pregnant women has remained relatively unchanged.

Alcohol intake during pregnancy can have a large range of outcomes on a fetus. Alcohol is a teratogen that affects the central nervous system, and there is no known "safe" level defined during pregnancy.[10-12] The teratogenic effects of alcohol can induce fetal malformations at any stage of pregnancy, as well as at low or high levels of alcohol intake, affecting the developing fetus to varying degrees, in both extent and severity. This depends on numerous factors, including the dosage and timing of alcohol intake in the pregnancy, genetics, age of the mother, parity, and nutritional factors.[4] Thus, it is not surprising that not all individuals exposed to similar amounts of alcohol during pregnancy have the same outcomes. Some children may be severely affected in multiple areas, and other children may have no apparent effects.

Fetal alcohol syndrome (FAS) is the most severe form of fetal damage from alcohol and refers to a distinct disorder with clinical features. Three distinct areas are required to be diagnosed as having FAS, including growth retardation, facial appearance, and central nervous system (CNS) problems.[4] Each component of the FAS diagnosis can range in severity according to the patient's age, environmental variables, and the quantity and quality of prenatal alcohol exposure.

In addition to FAS, the Institute of Medicine has identified three other diagnoses that are considered part of the FASD spectrum[14]:

Partial FAS. This describes people with facial anomalies and other symptoms of FAS without all the signs of FAS.

Alcohol-Related Neurodevelopmental Disorder (ARND). This refers to neurological defects, such as problems with communication skills, memory, learning ability, visual and spatial skills, intelligence, and motor skills. A child with ARND will not have all the physical features of FAS. Examples of ARND include speech delays, attention deficits, poor visual focus, and hyperactivity.

Alcohol-Related Birth Defects (ARBD). These are defects to organs, bones, or muscles. They may include abnormalities of the heart, eyes, ears, kidneys, and skeleton. Examples include holes in the heart, fused bones, and underdeveloped kidneys.

Only trained professionals can make a diagnosis. Teachers or relatives may identify a problem, but they cannot make the diagnosis of FASD.

Epidemiology

FAS. Estimates of the incidence of FAS vary significantly in different populations and with different types of research designs. Some of this variation is a valid reflection of actual differences in FAS rates between populations.[15] This is especially true in populations with large differences in maternal drinking behavior.[15] However, variance in FAS incidence between research studies also can be a function of the different research methods used to study the problem. Passive surveillance systems, which typically use hospital discharge data, tend to give lower estimates of FAS than clinic-based studies or active case ascertainment methods. A summary of various studies has reported that the overall prevalence of FAS in the United States is likely to be between 0.5 and 2.0 per 1,000 births.[15]

Disparities exist within FAS. "Heavy"-drinking women have the highest reported incidence of FAS. Heavy drinking is defined here as those consuming an average of 2 or more drinks per day, 5 to 6 drinks per occasion, a positive MAST score, or a clinical diagnosis of alcohol abuse. Children of women who fall in this category have an FAS rate of 4.3%.[5]

There is also a disparity in FAS with regard to race. The United States incidence of FAS in primarily Caucasian populations is estimated to be around 0.26 per 1,000 births.[5] The African-American incidence of FAS in the United States is much higher, at 2.29 per 1,000 live births. Thus the ratio of African-American to Caucasian incidence of FAS is 8.8:1, meaning that for every Caucasian baby born with FAS, almost 9 African-American babies are born with FAS. An additional disparity was reported in Alaska natives, with an incidence of FAS estimated between 3.00-5.20 per 1,000.[16]

Another high disparity in FAS occurs with regard to maternal socioeconomic status. Abel, 1995, estimated that the incidence of FAS in women in the United States with incomes of $10,000 or less for a family of three was 2.29 per 1,000 births.[5] Women of middle or high income were estimated to have an incidence of only 0.26 per 1,000 births. Children with FAS are frequently characterized by low socio-economic status.[2,17] Low socioeconomic status and heavy alcohol consumption are both associated with poor nutrition, stress, poor health, smoking, and the use of other substances[15,18-20] Although none of these factors is a cause of FAS, it is possible that they may exacerbate the effects of heavy alcohol intake, which may result in FAS.[5]

FASD. The true epidemiology of FASD is not known. Many cases of FAS go undetected at birth and even later in life.[14] Children with less severe phenotypes in the FASD continuum present an even greater diagnostic challenge because often the phenotypic characteristics are even more subtle. In addition many children are misdiagnosed with a multitude of other disorders. Attention deficit hyperactivity disorder, autism, major depressive disorder, or bipolar disorder are examples of common misdiagnoses.[21] Co-morbidities with other mental health problems are common in children with FASD and thus make diagnosis even more of a challenge. These less-severe types of FASD are much more common than FAS and may affect 1% or more of all children born in the United States.[22,23]

Alcohol Consumption During Pregnancy

The Centers for Disease Control and Prevention (CDC) estimates that more than half (53.7%) of nonpregnant women of childbearing age (18-44) have reported alcohol consumption in the past month, and approximately one in eight (12.1%) report binge drinking.[24] Furthermore, in the United States, almost half of pregnancies are unplanned.[25] For pregnant women, the CDC reported that the average annual percentage of any alcohol use was 12.2%, and of binge drinking was 1.9%. The highest percentages of pregnant women reporting any alcohol use were aged 35-44 years (17.7%), college graduates (14.4%), employed (13.7%), and unmarried (13.4%).[24]

The number of women who drink alcohol during pregnancy far surpasses the total number of children diagnosed with either FAS or FASD.[26] This means that not every child who is exposed to alcohol during pregnancy will have FAS or FASD. In addition, the degree of severity of FAS or FASD in an individual varies greatly from person to person. Several factors may contribute to this variation in severity of alcohol exposure to a child. These factors include, but are not limited to, the following[26,27]:

- Maternal drinking pattern
- Maternal age
- Parity
- Maternal metabolism differences
- Genetic differences in alcohol metabolism
- Timing of the alcohol exposure to the fetus
- Differences in the vulnerability of various brain regions
- Polydrug use.

Diagnosis of FASD

FASD is an umbrella term describing the range of effects that can occur in an individual whose mother drank during pregnancy. These effects may include physical, mental, behavioral, and/or learning disabilities with possible lifelong implications.[6] In most cases of FASD, the pathognomonic physical features are not present. This makes the diagnosis challenging at best and impossible at worst if a maternal drinking history is unknown. Although many articles discuss the behavioral phenotype of FASD, the clinical diagnosis remains problematic.[28] For these reasons, the discussion of diagnosis in this article will be limited to FAS. No specific and uniformly accepted diagnostic criteria are available for FAS. Several standards have been suggested over the past 20 years.[9,14,29] Although they have been widely used, their practical clinical applications are less than optimal. In 2004, a national task force published a set of suggested guidelines for the diagnosis of FAS.[7] These criteria are discussed below.

Fetal Alcohol Syndrome (FAS)

Dysmorphia. Clear insight into the recognition of alcohol as a teratogen was not described until 1968.[2] However, descriptions of the children of alcoholics noted as "born weak and silly ... shriv-

eled and old, as though they had many numbered years" appeared in the medical literature as early as the 1700s.[30] For the first time, in 1973, several investigators[3] described in detail the consistent pattern of malformations observed in the children of mothers who drank heavily during their pregnancies. These observations provided the criteria for a condition they termed FAS.

Their early studies focused on short palpebral fissures, maxillary hypoplasia, and the presence of epicanthal folds. Over the course of the next 30 years, additional features that were described included cardiac anomalies, hypoplastic nails, microcephaly, short nose, smooth philtrum with thin vermillion border, cleft lip, micrognathia, webbed neck, meningomyelocele, hydrocephalus, and hypoplastic labia majora.[13]

Because of the heterogeneity of expression for dysmorphic features related to prenatal exposure to alcohol, the general consensus is that diagnostic criteria should be limited to core facial dysmorphia.[31] This is based on human observational studies as well as experimental animal studies that have demonstrated fetal alcohol exposure disturbs cellular migration during organogenesis along the midline of the face.

The following dysmorphic facial features meet the dysmorphic criteria essential for FAS (based on racial norms):

• smooth philtrum (measured as 4 or 5 on lip-philtrum guide) (*see Figure 1*);

• thin vermillion border (measured as 4 or 5 on lip-philtrum guide);

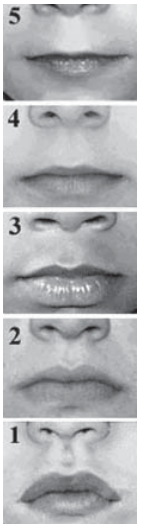
• small palpebral fissures (measured as < 10th percentile) (*see Figure 2*).

After puberty, these characteristic facial features can become more difficult to detect. However, recent findings indicate that these three features remain for the majority of individuals with FAS.

Growth Deficiency. Growth deficiency historically has been regarded as a major feature of FAS. The initial cases of FAS initially were assessed for failing to thrive. Abundant research in both humans and animals has demonstrated that alcohol can have an adverse impact on length and weight both prenatally and postnatally.[32-34] Unlike the facial anomalies, fetal growth is most significantly impacted by alcohol exposure in the last half of pregnancy. The parameters (height, weight, head perimeter) and the severity (2nd to 25th percentile) for assessing growth deficiency vary greatly in the literature. Current criteria for growth deficiency is the following: Confirmed prenatal or postnatal height and/or weight at or below the 10th percentile at any one point in time. These parameters should be adjusted for age, sex, gestational age, and race or ethnicity.[31]

Central Nervous System (CNS) Abnormalities. Multiple publications documenting the teratogenic effects of alcohol on the CNS have been in the medical literature over the past 30 years.[33-35] These congenital anomalies have been shown to result in a wide range of short-term and long-term behavioral and cognitive deficits. These neurobehavioral effects persist through affected individuals' lifetimes and have rendered many of them unable to live independently.[275] The CNS abnormalities included in the criteria for the diagnosis of FAS are categorized as structural, neurological, functional, or combinations of any or all.

Figure 1. Lip-philtrum Guide



The smoothness of the philtrum and the thinness of the upper lip are assessed independently. Scores of 4 or 5 are consistent with FAS. Reprinted with permission. © 2009 Susan Astley, PhD, University of Washington.

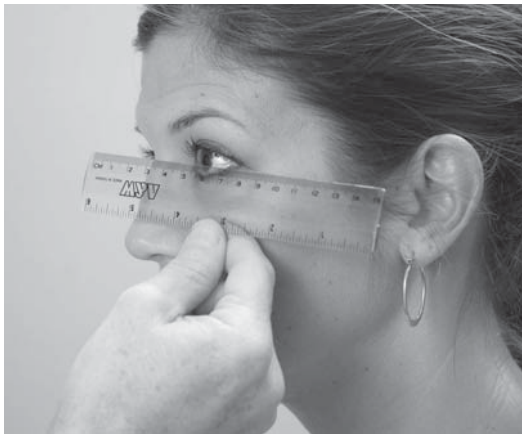
Structural. Structural CNS abnormalities associated with the diagnosis of FAS consist of two general criteria. First is a diminished occipitofrontal circumference (OFC). This is defined as < 10th percentile, adjusted for age and gender. In children with growth deficiency (height and weight < 10th percentile), the OFC should be disproportionately small: i.e., < 3rd percentile. The second criterion is clinically significant brain abnormalities that are detected through imaging techniques. Previously documented abnormal findings include reduction in the size and shape of the corpus callosum, cerebellum, or basal ganglia.[36,37]

Neurological. Numerous abnormal neurological findings have been associated with prenatal alcohol exposure.[13] These include seizures, visual motor difficulties, nystagmus, coordination problems, and problems with motor control. However, the etiologies of intra-partum or postnatal insult and fever must be ruled out prior to assigning alcohol as the cause.

Functional. The functional abilities affected by prenatal alcohol exposure vary greatly from person to person, depending on the amount of alcohol, timing of exposure, and the pattern of exposure (i.e., chronic vs. binge). Despite the inherent variation, the observed functional deficits correspond to multiple locations in the brain affected by exposure. To address this issue, functional effects may be assessed in two ways: global deficits or deficits in functional domains (secondary disabilities). To meet the diagnostic criteria for FAS, the individual must have one or the other.

Global cognitive deficit is defined as decreased IQ (below the 3rd percentile) or significant developmental delay in children too young for IQ assessment. A decrease in performance in these assessments assumes multiple functional domains have been affected.

Figure 2. Measurement of the Palpebral Fissures



The above image demonstrates the correct technique measuring the palpebral fissure.

Deficits (one standard deviation below the mean for standardized testing) in three or more specific functional domains. These are described below:

• Cognitive or developmental discrepancies: learning disabilities (particularly in math and/or visual-spatial deficits); uneven profile of cognitive skills; poor academic achievement; discrepancy between verbal and non-verbal skills; and slowed movements or reaction to people and stimuli.

• Executive functioning deficits: poor organization, planning, or strategy use; difficulty grasping cause and effect; difficulty following multistep directions; difficulty changing strategies or thinking of things in a different way; poor judgment; and inability to apply knowledge in a new way.

• Motor functioning delays or deficits: delayed motor milestones; difficulty writing or drawing; clumsiness; balance problems; tremors; poor dexterity.

• Attention and hyperactivity problems: easily distracted; difficulty in calming down; overly active; difficulty completing tasks; trouble with transition. Of note, many children with FAS often receive the diagnosis of attention deficit hyperactivity disorder (ADHD). Although this diagnosis can be applied, research has shown that the attention problems of children with FAS do not fit the classic pattern of ADHD.[38] Individuals with FAS tend to have difficulty with the encoding of information and flexibility aspects of attention, whereas children with ADHD typically display problems with focusing and sustaining attention.[38] A recent publication provides a screening tool for distinguishing the behavioral characteristics between the two conditions.[28]

• Social skills problems: lack of stranger fear; naivete and gullibility; inappropriate choice of friends; often scapegoated; inappropriate sexual behaviors; difficulty understanding the perspective of others; and clinically significant inappropriate initiations or interactions.

• Other potential domains: sensory problems (tactile and oral); pragmatic language problems; memory deficits; and difficulty responding to normal parenting practices (not understanding cause and effect).

Ideally, the above described deficits should be established by a trained professional using appropriate standardized neuropsychological testing. In many cases, this type of testing is not readily available. In these situations, clinicians are encouraged to supplement their observations with standardized testing offered in early intervention programs and public schools. It must be emphasized that, when evaluating an individual for FAS, using clinical judgment without the benefit of psychometric testing can result in an incorrect diagnosis or an inappropriate treatment plan.

Maternal Alcohol Exposure

Documentation and confirmation of prenatal alcohol exposure is perhaps the most challenging of the criteria to obtain in making the diagnosis of FAS. Admission of alcohol use is stigmatizing to the mother. This information must be collected in a non-threatening, non-judgmental fashion. In the case of the mother actively drinking during pregnancy, obtaining accurate information about the amount and frequency of consumption is frequently not possible. The most difficult clinical scenario is when an individual is being evaluated and there is no information about the index pregnancy. This frequently occurs in foster care or adoptive homes.

In situations where it can be accurately determined that no alcohol had been consumed from conception to birth, the diagnosis of FAS is ruled out.

Categories for qualifying as prenatal alcohol exposure are as follows:

• Confirmed prenatal alcohol exposure: requires a history of alcohol exposure by the birth mother during the index pregnancy based on clinical observation; self reports; report by a reliable informant; medical records documenting positive blood alcohol levels or alcohol treatment; or other social, legal, or medical problems related to alcohol consumption during the index pregnancy.

• Unknown prenatal alcohol exposure: where there is neither confirmed presence of exposure nor confirmed absence of exposure.

In summary, the diagnosis of FAS requires the presence of all three of the following findings:

• documentation of all three facial abnormalities (smooth philtrum, thin vermillion border, small palpebral fissures;

• documentation of growth deficits;

• documentation of CNS abnormalities (structural, neurological or functional, or combination thereof).

The confirmed or unknown status of alcohol exposure is not required for the diagnosis of FAS to be entertained. As stated above, in the confirmed absence of prenatal alcohol exposure, the diagnosis of FAS is ruled out.

Treatment

Unfortunately, because the alcohol-induced CNS abnormalities create permanent disabilities, there is no cure for FAS. However, effective treatment is possible. Since the CNS damage, symptoms, secondary disabilities, and needs vary greatly from

one individual to the next, not one form of treatment works for everyone. Additionally, because research in the area of FAS treatment is in its infancy, relatively speaking, well-defined therapeutic modalities are still evolving. Nevertheless, human studies, clinical observations, and family experiences concur that the common features that most often result in successful treatment include early diagnosis; a loving, nurturing, stable environment; involvement of special education and social services; and absence of violence in the individual's life.

When describing the treatment of FAS, it can be helpful to divide the discussion into four general areas: early intervention; child-focused; adolescents; and adults.

Early Intervention. Current research indicates that early intervention has the potential to ameliorate at least some deficits found in individuals with FAS.[39] If the diagnosis of FAS is suspected antenatally, the infant can qualify for early intervention at the time of birth. Early interventionists can be the first to confirm the diagnosis, alert caregivers to emerging learning and behavior problems, and connect families with needed services. Specific services for the child include direct intervention with evidence-based early education curricula focusing on math and handwriting skills and supportive services from occupational therapists and speech pathologists. Families are taught skills to support and participate in the child's learning, encouraged to join established support/advocacy networks, and provided alcohol treatment, if needed.

Child-Focused. Child-focused treatment addresses the specific functional deficits that have been diagnosed in the affected individual. As stated earlier, these can include deficits in attention and executive function, social skills, and behavioral regulation. Modalities that have been suggested to remediate these deficits are cognitive control techniques, friendship skill-building groups, calming techniques, social skills groups, and neurobehavioral feedback.[40] A recent study has demonstrated the potential for computer training in older children as a powerful resource for training in life and social skills.[41]

Adolescents. The life phases of adolescence are an especially difficult time for those with FAS, given the complex but often subtle neurodevelopmental disabilities they possess. Unfortunately, this critical period in their lives often is omitted in the continuum of FAS intervention. Despite this reality, there are specific treatment options suggested for this unique population of individuals.

Group therapy for teens and young adults with FAS is a new and promising direction in treatment. These groups have a central focus on learning and practicing social skills. Teens are taught how to appropriately establish intimacy and build trusting, positive peer relationships. These groups also provide appropriate and literal education on topics such as substance use, dating, and sexuality.

Support and resources for adolescents and younger adults are clearly important and necessary. In many communities, these are not readily available. The option of regionally sponsored retreats for teens with FAS is now a growing trend in some states. Generally, these retreats require that the diagnosed individual bring along a support person. As the numbers of teens diagnosed with FAS increases, so the opportunities for them to gather together will become more warranted and hopefully more available.

Adults. The functional deficits that are diagnostic of FAS are also described as secondary disabilities, with the primary disability being the CNS birth defect caused by prenatal alcohol exposure. These disabilities manifest clinically as mental health problems. The most common presentations are depression, attention deficit problems, panic attacks, auditory and visual hallucinations, and suicide threats and attempts. With the exception of attention deficit problems, all of these increase with age.[27] Whereas much of the treatment focus in childhood is on addressing the developmental disability, in the adult the approach should be treating the patient as an individual with a dual diagnosis.

In the adult, treatment is usually multimodal. Many different types of therapies are applied over time as they are needed. These may include individual counseling, family therapy, special education, and psychopharmaco-therapy.

In regard to medical intervention, since this group of patients has deficits in both neuroanatomy and neuro-chemistry, their responses to medications can be quite unpredictable. It is wiser to identify areas of stress in the individual's environment and make changes there, as opposed to immediately treating the symptoms with medication.

Another approach to treatment of the adult with FAS is using an advocacy model.[27] This method assumes that someone is needed to actively mediate between the environment and the person with FAS. The advocate (family member, friend, case manager, therapist) functions in three basic areas for the individual: interpreting FAS and the disabilities that arise from it and explaining it to the environment in which the patient operates; engendering change or accommodation on behalf of the patient; assisting the patient in developing and reaching attainable goals.

The ultimate goal of this model is that, with the help of a caring advocate, the individual with FAS negotiates life tasks and learns necessary skills.

Prevention

Fetal alcohol spectrum disorders are 100% preventable, as they do not occur among children born to women who abstain from alcohol during pregnancy. Prevention of FASD, therefore, is the most effective strategy for decreasing the impact of this health problem. There is no known safe level of alcohol consumption during pregnancy, so it is prudent for women to completely avoid alcohol while pregnant. In addition, if a woman is planning to get pregnant or is sexually active and not using effective birth control, she should avoid alcohol consumption because she could be pregnant and not know for several weeks or more.

Prevention of FAS in the United States primarily began in 1981 when the Office of the Surgeon General issued an advisory that pregnant women or women planning a pregnancy should abstain from drinking alcohol.[42] In 2005, the U.S. Surgeon General issued an updated advisory that advises women not to drink alcohol if they are pregnant, planning to become pregnant, or at risk of becoming pregnant. In addition, warning labels have been required on alcoholic beverage containers sold in this country since 1990.

Table 1. FASD Prevention Strategies

Primary Prevention
- Engage in education on the adverse effects of alcohol on the fetus and FASD with all women of childbearing age and their partners.
- Screen all female patients of childbearing age about their use of alcohol.
- Use promotional materials in offices and as handouts for patients.
- Have a comprehensive list of alcohol treatment services within the community and refer clients to these services when necessary.
- Discuss and increase access to contraceptive strategies with all women of childbearing age and their partners.

Secondary Prevention
- Identify women who are using alcohol during pregnancy with a recommended screening tool (TACE, TWEAK) and assess the level of risk.
- Counsel pregnant women who are using alcohol about the effects on the fetus and their own health.
- Advise pregnant women about the benefits of stopping or reducing the use of alcohol at any time during pregnancy.
- Refer women who are using alcohol for appropriate treatment.

Tertiary Prevention
- Identify those women at high risk in future pregnancies.
- Refer women at risk for appropriate treatment.
- Counsel pregnant women who are using alcohol about the effects on the fetus and their own health.
- Provide contraceptive counseling.

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Unfortunately, the warning labels have primarily resulted in a reduction of alcohol consumption in those women who are considered light drinkers.[43] Despite these efforts, alcohol use among pregnant women has remained relatively unchanged from 1991-2005.[24]

To prevent FASD, no single group, organization, community, ministry, or level of government can deal effectively with the problem on its own. Broad-based efforts are required, with policy interventions that affect everyone in addition to more specific community-level interventions that may target specific populations. Prevention strategies is this paper, however, will focus on those that a physician or other health care professional can engage in.

Prevention is the first line of defense against the effects of alcohol in pregnancy and should include the following:

• Primary prevention: These are interventions that avert a health problem prior to its occurrence. For FASD, an example of this could be informing the public, and particularly women of childbearing age, about the dangers of drinking during pregnancy.

• Secondary prevention: These include interventions that seek to reduce the severity and/or duration of the health problem. For FASD, an example would include alcohol screening and early intervention programs and services for pregnant women who would be at risk for having a child with FASD.

• Tertiary prevention: These are interventions that would prevent the recurrence of the health problem and attempt to lessen the impact of the health problem. For FASD, an example would be an intervention targeted at women who have already had a child with a FASD. Another example could include a therapy designed specifically for a child with FASD.

Table 2 provides FASD prevention strategies adapted from the Canadian Child Adolescent Psychiatric Review that a physician's or health provider's practice could use to assist in the prevention of FASD.[44]

Conclusion

Physicians and other health care providers can have a large impact on how well fetal alcohol spectrum disorders are diagnosed and treated, as well as play a crucial part in prevention efforts. Improvement in these areas could reduce the incidence of FASD and increase the quality of life for those who have an FASD.

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Physician CME Questions

1. Which population below has the highest prevalence of FAS?
   A. people with low income
   B. those of African-American race
   C. those of Alaskan native race
   D. children of mothers who were heavy drinkers
   E. mothers younger than 18 years of age

2. Which of the following would *not* be a prevention strategy for FASD?
   A. giving educational pamphlets to pregnant women on the effects of alcohol on a fetus
   B. referring the mother of a child with FAS to an alcohol treatment service
   C. screening a pregnant woman for alcohol use at a routine prenatal visit
   D. calculating the prevalence of FASD in a community

3. All of the following criteria are included in the diagnosis of FAS *except*:
   A. dysmorphic facial features
   B. congenital heart disease
   C. status of prenatal alcohol exposure
   D. growth deficiency

4. All of the following statements regarding the treatment of FAS are true *except*:
   A. Effective treatment is possible.
   B. Treatment must be individualized.
   C. Treatment for FAS is well-defined.
   D. Successful treatment is optimized by early diagnosis.

CME Answer Key: 1. D; 2 D; 3. B; 4. C

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The Practical, Peer-Reviewed Journal for Primary Care and Family Physicians

2009 Subject Index

Covering Volume 15

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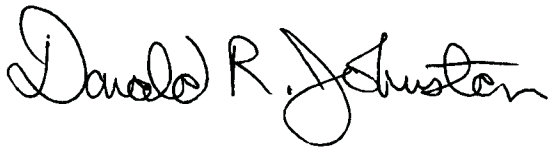

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The relationship of FPG and A1c to diabetic retinopathy

Source: Cheng YJ, et al. Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population. *Diabetes Care* 2009;32:2027-2032.

THE IDEA THAT A1c MIGHT BE A REASONABLE metric to make the diagnosis of diabetes has been kicking around for more than a decade. Only very recently has there been advocacy from the ADA that A1c may be an acceptable method for diagnosis of diabetes (A1c ≥ 6.2%); a primary reason for this shift in perception is the widespread adoption of a nationally standardized A1c testing method. Ultimately, diagnosis is intended to go beyond simply categorizing an individual as diabetic or non-diabetic; rather, it is intended to predict risk for important complications of diabetes like retinopathy.

The NHANES (National Health and Nutrition Examination Survey) is a cross-sectional sampling of non-institutionalized civilian adults. From the NHANES 2005-2006 study population, a group of adults age ≥ 40 years had assessment of retinopathy, A1c, and fasting plasma glucose (FPG).

There was a steep increase in frequency of retinopathy at an A1c ≥ 5.5%. Although a similar increased risk was seen at a FPG of 126 mg/dL, overall, the A1c was a better predictor than FPG. Since A1c may be obtained whether or not the subject has fasted, it may become a more convenient (as well as more sensitive) method than FPG for identifying risk of retinopathy. ■

Getting the most bang for your buck with lipid measurement

Source: The Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993-2000.

THE EMERGING RISK FACTORS COLLABORATION collected data from prospective observational studies of persons without CV disease at baseline (n = 69 studies, with 302,430 participants). Lipid fractions measured in these studies included LDL, HDL, apo B, and apo A1. Risk for incurring CV endpoints was stratified for each lipid fraction.

Triglycerides have always been the lipid fraction demonstrating the weakest association to CVD endpoints. In this data set, although the unadjusted hazard ratio for triglycerides demonstrated increased hazard, adjusted hazard ratios were not convincing. In contrast, subjects with the lowest HDL levels showed an almost 3-fold greater hazard ratio for CV events than those in the highest third. The ratio of apo B:apo A1 was also an important CV risk predictor.

Interestingly, measurement of total cholesterol, HDL, apo B, and apo A1 in the non-fasting state did not appear to appreciably alter their predictive value. Sufficient information for risk prediction, according to these data, is obtained by simply measuring cholesterol levels (total and HDL). Additionally, the authors were not able to identify any significant additional CV risk prediction by adding triglyceride levels to their calculations.

The simplicity of focusing upon total and HDL cholesterol, and being able to use non-fasting results, may enable clinicians to more readily gather predictive information on a wider population of patients. ■

Nortriptyline, gabapentin, or both for neuropathic pain

Source: Gilron I, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: A double-blind, randomised controlled crossover trial. *Lancet* 2009;374:1252-1261.

NEUROPATHIC PAIN (NPN), SUCH AS post-herpetic neuralgia or diabetic peripheral neuropathic pain, often requires what has been described as rational polypharmacy: the combination of multiple agents in an attempt to gain maximum therapeutic advantage while minimizing adverse effects. Both nortriptyline and gabapentin have achieved some success in modulation of NPN as monotherapy. Since the mechanism of action of these agents is complementary, a trial of their combination has intellectual appeal. When choosing among antidepressants for analgesic effects, norepinephrine re-uptake inhibition appears to be a critical component. Hence, SSRIs have minimal effect, but tricyclics (e.g, amitriptyline, nortriptyline), SNRIs (e.g., duloxetine, venlafaxine), and highly selective norepinephrine re-uptake inhibitors (e.g., milnacipran) effectively reduce pain.

Combination nortriptyline and gabapentin provided significantly greater pain reduction than either agent alone. No serious adverse effects were seen in either mono- or combination therapy. Clinicians are already commonly applying combination therapies to neuropathic pain syndromes; it is gratifying to encounter sound evidence supporting this practice. ■

Which insulin regimen for type 2 diabetes

Source: Holman RR, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; 361:1736-1747.

THE MOST RECENTLY PUBLISHED ADA/EASD consensus algorithm for management of type 2 diabetes (DM2) suggests that when the combination of metformin and lifestyle is insufficient to control diabetes, either sulfonylurea (if close to goal) or insulin is the most well-validated next step. Because there are many different insulins to choose from, the clinician may be uncertain whether basal insulin (i.e., detemir, glargine, NPH), prandial insulin (i.e., regular insulin or rapid-acting insulin analog), or biphasic insulin (a combination containing a basal as well as prandial insulin) should be preferred.

Holman et al performed a 3-year trial in DM2 subjects (n = 708) not at A1c goal with the combination of metformin and a sulfonylurea. Subjects were randomized to biphasic insulin aspart (BIA) bid, prandial insulin aspart (PIA) tid, or insulin detemir (DET) qd (some received detemir bid).

At 3 years, there was no statistically significant between-group difference in A1c attained. Hypoglycemia was least frequent in the DET group, and most common in the PIA cohort. Weight gain was least in the DET group, and greatest in the PIA group.

All regimens were successful in attaining goal A1c. Because hypoglycemia and/or weight gain are often deal breakers for our patients, basal insulin regimens may be preferred. ■

Cardioprotective effects of ACE inhibitors in African American men

Source: Papademetriou V, et al. Protective effects of angiotensin-converting enzyme inhibitors in high-risk African American men with coronary heart disease. *J Clin Hypertens* 2009;11: 621-626.

THE HOPE TRIAL CONVINCED MANY experts that midlife adults (age ≥ 55 years) with existing vasculopathy (history of CAD, CVD, diabetes and CV risk factors) will have improved outcomes on an ACE inhibitor (ramipril, to be specific). There is controversy about whether African Americans achieve similar risk reduction as other ethnicities; for instance, in the SOLVD CHF trial, retrospective analysis suggested less benefit for some endpoints in African Americans.

Papademetriou reviewed electronic records from the Washington, DC, VA Medical Center to study African American study subjects who had CAD documented by catheterization (n = 810). Subjects were parsed into those who had vs had not been treated with an ACE inhibitor.

Over a study period of 3-10 years (mean, 6.8 years), the relative risk reduction for CAD mortality was more than 30% in those treated with ACE inhibitors. All-cause mortality was 80% higher in African American patients who had *not* been treated with ACE inhibitors. Because many African American patients have relatively low renin levels, some clinicians have doubted whether CV benefits would be readily achieved with ACE inhibitors. This data analysis suggests substantial benefit from ACE inhibitor treatment in African Americans with CAD. ■

Missed opportunity: Aldosterone antagonists in heart failure

Source: Albert NM, et al. Use of aldosterone antagonists in heart failure. *JAMA* 2009;302:1658-1665.

THE SEMINAL RALES TRIAL (RANDOMized Aldactone Evaluation Study), in which patients with NYHA Class III-IV systolic heart failure received either aldactone or placebo in addition to standard-of-care treatment (e.g., ACE inhibitors, beta blockers, digoxin) indicated that the utilization of this well tolerated, inexpensive treatment could reduce mortality by as much as 30%.

One might anticipate that such benefits would result in widespread utilization of aldosterone antagonists in heart failure.

Albert et al reviewed data from more than 200 U.S. hospitals, encompassing 43,625 patient admissions for heart failure over the 2005-2007 time period. By this time, the RALES data were more than 5 years old. Contraindications to this life-saving treatment are few, with hyperkalemia being the most common.

According to their analysis, less than 33% of patients with heart failure who were eligible for treatment with an aldosterone antagonist (i.e., without contraindications) received one. With proper monitoring, aldosterone antagonist therapy reduces risk, is safe, and is well tolerated. Although aldosterone antagonist use improved over time (from a baseline rate of 28% to an end-of-study rate of 34%), much opportunity of reduction of mortality was missed. ■

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Niacin Beats Ezetimibe Head to Head

In this issue: *Statin and niacin increase HDL-C, omeprazole reduces effectiveness of clopidogrel, darbepoetin increases risk of stroke, statins decrease risk of gallstone disease, FDA Actions.*

Statin plus niacin or ezetimibe?

Raising HDL-cholesterol (HDL-C) with niacin plus a statin is superior to lowering LDL-cholesterol (LDL-C) with ezetimibe plus statin in reversing atherosclerosis according to the widely reported ARBITER trial published on-line in the *New England Journal of Medicine* in November and simultaneously reported at the American Heart Association meeting in Orlando, FL. The trial enrolled more than 200 patients with coronary heart disease or a coronary heart disease equivalent who were receiving long-term statin therapy with an LDL-C < 100 mg/dL along with an HDL-C < 50 mg/dL for men or 55 mg/dL for women. The patients were randomly assigned to receive extended-release niacin (target is 2000 mg/day) or ezetimibe (10 mg/day). The primary endpoint was the difference in change from baseline in mean and maximal carotid intima-media thickness after 14 months. The trial was terminated early in July of 2009. Both drugs were effective in their roles — the mean HDL-C in the niacin group increased by 18.4% over the 14-month study period ($P < 0.001$) and the mean LDL-C level in the ezetimibe group decreased by 19.2% ($P < 0.001$). Niacin significantly reduced LDL-C and triglycerides as well, while ezetimibe lead to a reduction in HDL-C and triglycerides. Niacin was superior to ezetimibe in reducing the primary endpoint, leading to a reduction of both mean ($P = 0.001$) and maximal carotid intima-media thickness ($P \leq 0.001$ for all comparisons). Paradoxically, greater reductions in LDL-C seen with ezetimibe were significantly associated with increases in the carotid intima-media thickness. The incidence of major cardiovascular events was also lower in the niacin group than in the ezetimibe group (1% vs 5%; $P = 0.04$ by the chi square test) (published on-line at: www.nejm.org; Nov. 15, 2009).

The study has received enormous attention not only because of the primary endpoint, but also because of the significant reduction in major adverse cardiac events in the niacin group, even though the numbers were quite small. At least one editorialist laments the early termination of the study and feels that it is impossible to make recommendations regarding the "adjuvant agent of choice" based on the small numbers (The HALTS Trial — Halting Atherosclerosis or Halted Too Early; published on-line at: www.nejm.org; Nov. 15, 2009). Still, this study provides enough evidence to consider adding niacin to a statin in patients who are at risk of or have low HDL-C. It also deals another blow to ezetimibe (Zetia®) and its partner drug ezetimibe/simvastatin (Vytorin®).

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Omeprazole's effect on clopidogrel

The FDA has issued a warning regarding the combination of clopidogrel (Plavix®) with omeprazole (Prilosec®) citing new data that suggest that the combination reduces clopidogrel's effectiveness by about half. Studies reported in 2009 suggested that omeprazole may block clopidogrel's conversion to its active metabolite via CYP2C19, an enzyme that is inhibited by omeprazole. New studies requested by the FDA from the manufacturers confirm a significant interaction between the two drugs, which can significantly hinder clopidogrel's ability to prevent platelet aggregation in patients at risk for heart disease. Omeprazole and clopidogrel are commonly prescribed together to prevent GI bleeding. At this time it is unclear whether this interaction extends to other proton pump inhibitors, although physicians are encouraged to avoid a combination of clopidogrel with esomeprazole (Nexium®, cimetidine (Tagamet®), and other drugs known to inhibit CYP2C19. The FDA is recommending that patients who need GI protection in conjunction with clopidogrel may safely use ranitidine (Zantac®), famotidine (Pepcid®), nizatidine (Axid®), or oral antacids.

Darbepoetin and risk of stroke

Darbepoetin alfa (Aranesp®) is commonly used in patients with chronic kidney disease and diabetes for the treatment of anemia. A new study suggests that the drug may be associated with increased risk of stroke in this patient population. More than 4000 patients with diabetes, chronic kidney disease, and anemia were randomly assigned to darbepoetin alfa to achieve a hemoglobin level of 13 g/dL or placebo with rescue darbepoetin alfa if hemoglobin levels dropped < 9 g/dL. The primary endpoints were the composite outcomes of death or cardiovascular event, and death or end-stage renal disease. After a follow up of 2.5 years, darbepoetin alfa was ineffective at preventing either primary outcome, and, more importantly, the rate of fatal or nonfatal stroke occurred almost twice as often in the treatment group (101 patients assigned to darbepoetin alfa vs 53 patients assigned to placebo; HR, 1.92; 95% confidence interval, 1.38-2.68; $P < 0.001$). The authors conclude that the use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis did not reduce the outcome of death, cardiovascular events, or renal events, but was associated with increased risk of stroke. For many "this risk will outweigh the potential benefits" of the drug (*N Engl J Med* 2009;361:2019-2032). Erythropoiesis-stimulating agents have come under fire in the treatment of cancer-associated anemia, and now in renal patients as well. As pointed out in an accompanying editorial, the risks and benefits of these agents must be weighed, namely an increased risk of stroke vs a perceived improvement in quality of life (*N Engl J Med* 2009; 361:2089-2090).

Statins and gallstone disease

Statins have been shown to reduce the risk of cardiovascular disease and death from all causes. Now another potential benefit is being reported: Statins may reduce gallstone disease. Utilizing a large patient database from the United Kingdom, researchers looked at the risk of developing gallstones followed by cholecystectomy in relation to exposure to lipid-lowering agents. The longer patients took statins, the lower the risk for gallstone disease, with patients who had filled 20 or more prescriptions noticing 36% reduction in risk (AOR, 0.64; 95% confidence interval, 0.59-0.70). The authors conclude that long-term use of statins is associated with a decrease risk of gallstones followed by cholecystectomy (*JAMA* 2009;302:2001-2007).

FDA Actions

The FDA has approved a new topical treatment for the treatment of post-herpetic neuralgia (PHN). The capsaicin 8% patch must be applied to the skin by a health care professional since placement may be quite painful, requiring the use of a local topical anesthetic. The patch is applied for one hour during which patients must be monitored, including observation for increases in blood pressure. The patches may be cut to conform to the area of pain and up to 4 patches may be used. The one-hour application is reported to provide up to 12 weeks of reduced pain from PHN. The capsaicin 8% patch will be manufactured by Lohmann Therapie-Systems and distributed by NeurogesX as Qutenza™.

The FDA has approved romidepsin for the treatment of cutaneous T-cell lymphoma in patients who received at least one prior systemic therapy. The drug is a histone deacetylase inhibitor, the first of a new class of antineoplastics. Romidepsin will be marketed as Istodax® by Gloucester Pharmaceuticals. ■