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COMMENTARY LETTER

Is it Time for Newborn Screening for Fetal Alcohol Spectrum Disorders: A Commentary

K. A. Pass, G.J. Mizejewski

Abstract: *Fetal Alcohol Spectrum Disorder (FASD) is one of the most common causes of acquired mental retardation in the United States and worldwide. The fetal brain is highly susceptible to the teratogenic effects of alcohol from maternal consumption during pregnancy resulting in newborns with mental deficits and congenital malformations. FAS diagnosis is difficult to diagnose in newborns where distinct anatomical defects are not apparent from mothers of moderate to light alcohol use. Hence, medical diagnoses are often not ascertained until mid-childhood after irreparable brain damage has already occurred. Such infants will have been deprived of available socioclinical interventions, trainings, measures, and future treatments that may someday be implemented soon after birth. Presently, there are no FASD newborn biomarker screening programs in place despite cost benefit analyses revealing an annual societal cost of \$1.3 million per FASD incident case. Since newborn biomarkers have been reported in the biomedical literature, can we afford not to implement newborn screening for FASD?*

Key words: *newborn, alcohol, cost/benefit, mental retardation, screening, prevalence*
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Alcohol is the most widely used drug in the world and accounts for 4% of the global disease burden [1]. Alcohol is a teratogen that induces a variety of abnormalities in the fetus, manifesting as brain and craniofacial defects depending on duration and magnitude of alcohol exposure [2]. The fetal brain appears to be particularly vulnerable to alcohol, and maternal alcohol consumption during pregnancy results in a spectrum of fetal developmental disorders first described as fetal alcohol syndrome (FAS). FAS is one of the most common causes of acquired mental retardation in the western world [3] and is now referred to as Fetal Alcohol Spectrum Disorder (FASD) which includes physical, clinical, and behavioral effects.

The gross anatomical malformations of FASD can encompass body weight and head size deficits, brain volume decreases, microencephaly, skeletal long bone and metacarpal defects, oral-palate size reductions, and post-axial ectrodactyly [4]. The tissue/nerve cell sites targeted by alcohol include the sympathetic nerve cell networks, cerebellum, brain ventricles, cerebral cortex, neuronal outgrowths, and synaptic circuitry [5].

Unfortunately, the diagnosis of FASD is usually not made until several years following birth, when alcohol damage has become irreversible and permanent. Societal and clinical interventions have been developed, and could be implemented if diagnosis were confirmed during the immediate postnatal period. Examples of such agents and/or procedures include: dietary supplementations such as zinc, fish oils, folic acid and vitamin E; rehabilitative motor skills training;

special handling procedures; memory exercises; environmental enrichment; educational exposures; behavioral phenotyping; mental capability testing; parental counseling; speech/language therapy; mental training exercises; and behavior modification [7]. Such treatments cannot reverse the effects of FAS, but can benefit the child by limiting mental impairments, improving health care delivery, and enriching the educational (learning) environment. Thus, the rationale for screening and early detection of alcohol-exposed newborns is that infants can receive timely diagnosis and societal and clinical treatments, at the earliest possible age when these will be most

K.A. Pass, Ph.D. and G.J. Mizejewski*, Ph.D.*

**Division of Translational Medicine, Wadsworth Center,
 New York State Department of Health, Empire State
 Plaza, Albany, NY 12201*

Corresponding Author: G.J. Mizejewski, Ph.D.

E-mail: mizejew@wadsworth.org

Phone: 518-486-5900

Fax: 518-402-5002

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beneficial.

FASD diagnosis in the newborn is a difficult task, especially when clear anatomical defects are not apparent, as may be the case in infants born to mothers who had medium to light alcohol use [7]. Such women give birth to infants with masked signs of cognitive, behavioral, and learning/memory impairments that will later surface as FASD. Studies using magnetic resonance imaging and other scanning modalities have shown that FASD children, with or without obvious facial defects, nevertheless still have abnormal brain anatomy and chemistry [8]. If the condition is undetected, FASD infants will be deprived of the available postnatal interventions, trainings, and measures that can be implemented soon after birth, to ameliorate and mitigate neurobehavioral deficits.

The age of medical assessment and diagnosis of FASD following birth can range from 1.0 to 8.0 or more years of age [9]. The FASD facial manifestations are easiest to recognize in mid-childhood but more difficult to observe in newborns [10]. Ethnically, the prevalence of FASD appears highest in American Indians and African Americans, followed by Hispanics, Caucasians, and Asians [11-13]. Although prevalence rates (PRs) vary by geographic area of the USA, the PR can approach 1 in 500 live births in some metropolitan areas, and 1 in 250 in American and Alaskan native localities [14-15]. The annual estimates of economics based on 3 – 4,000 FASD live births per year, has been reported to be a total over a \$1.0 billion, a figure which includes hospital visits, institutionalizations, mortality, reduced or lost productivity, premature deaths, and extensive caregiver services [16-17]. Projected future economic losses for both adult alcoholics and the affected FAS children/offspring could encompass costs of health-aid services, crime, motor vehicle crashes, fire destruction, crime victim losses, incarceration, and lifetime careers of crime [18]. The annual societal cost of FAS has been calculated as \$1.3 million per incident case [19].

For practical and economic reasons, governmental institutions and agencies do not usually screen for diseases which they cannot treat. However, during the last decade, FASD-related clinical treatments and medicine-based therapeutic studies have begun to appear in the medical literature, albeit some are based on FAS animal models. A variety of drug treatment options are presently in pre-clinical trials and lie at the threshold of potential biochemical therapies for FASD-identified newborns and infants. These drugs include the following: isapirone and buspirone, serotonin agonists; vinpocetine, phosphodiesterase inhibitor; MK-801, antagonist of n-methyl-d-aspartate (NMDA); Eliprodil, a selective antagonist of NMDA; EUK-134, a mimetic of superoxide dismutase/catalase; Bay-11-

7082, an inhibitor of NFkappa-B; vasointestinal, neurotrophic and neuroprotective peptides; and cholinergic muscarinic M1 agonists [20-22]. Investigators have recently reported that prenatal and postnatal administration of 8-9 mer neuropeptides can arrest developmental delays and learning abnormalities showing therapeutic potential in the prevention of further developmental deficits in FAS animal models [23]. One clinical study using adult alcoholic inpatients further showed that neurokinin-1 receptor antagonism was a beneficial therapeutic treatment for alcohol addiction [24].

Worldwide, there are no FAS newborn biomarker screening programs presently in place to identify this major cause of acquired mental retardation in the newborn; this is especially relevant since the manifestations of FASD are masked and/or concealed during pregnancy with moderate-to-light alcohol consumption. Even in two states (Washington and Wisconsin) utilizing only epidemiological monitoring, more efficient detection of FASD infants and clinical interventions have been reported [25-26]. In New York State, about 60% of newborns reported to a birth defects registry were later confirmed as FASD children based on a more intense surveillance (see reference 10).

Aside from the detection of ethyl esters in newborn meconium for alcohol exposure, no biochemical markers are in place today for FASD screening [27], even though newborn detection and diagnosis could increase adult lifetime earnings by \$26,400/year resulting in a gain of \$65,874 per quality-adjusted life years (see reference 19). Multiple biomarkers of FASD have been previously described in the literature [28-29], some of which are presently in use in prenatal screening programs. A list of some of these potential newborn screening biomarkers for FASD include: 1) Insulin-Like Growth Factor-1 (IGF-1, Somatomedin-C); 2) Human Growth Hormone; 3) Alpha-fetoprotein; 4) Brain-Derived Growth Factor; 5) Glial Fibrillary Acidic Protein; 6) Myelin Basic Protein; 7) Myelin-Associated Glycoprotein; 8) Serotonin (5HT1A); 9) Activity-Dependent Neurotrophic Factor; 10) Activity-Dependent neuroprotective factor; 11) Alpha-1-antitrypsin; 12) B-chain haptoglobin; 13) Alcohol Dehydrogenase; and 14) Retinol-binding protein (see References 25-27). Commercially-produced antiserum for many of these biomarkers are already available.

A potential candidate panel for biomarkers could be selected for newborn screening based on their relevance and previous identification with FASD in the medical literature. Five to seven candidate biomarkers, as performed in prenatal screening, could be selected from the preceding paragraph [28-30]. These could

include: 1) Serum Retinol Binding Protein; 2) Alcohol Dehydrogenase (ADH4); 3) Glial Fibrillary Acidic Protein; 4) Somatomedin-C; 5) Growth Hormone; 6) Brain-derived Neurotrophic Factor; and 7) Alpha-fetoprotein. Utilizing novel technologies for simultaneously testing multiple biomarkers [30], such candidate biomarkers could be assembled for newborn screening based on their relevance and previous utility with FASD detection. Interventions, treatments, and potential drug therapies for FAS could be considered if newborn screening feasibility and cohort studies were in place. Until that time, the identification of FASD in newborns will continue to remain a major public health need in the USA and throughout the world.

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