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Fetal Alcohol Spectrum Disorders: When Science, Medicine, Public Policy, and Laws Collide

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Historically, alcohol has been used for different purposes including as a part of religious observances, as a food, at times as a medicine and its well-known use as a beverage. Until relatively recently these purposes have not changed and have at times been at odds with one another, resulting in collisions among policies and practices in science, medicine, public policy and the law. One area in which this has been particularly true is that of fetal alcohol spectrum disorders (FASD) where the adverse consequences of consumed alcohol on children in the womb and after birth may have been observed since antiquity, but the actions taken based on such observations have been influenced as much by the socio/cultural/political context of the times in which they were made as by evidence of harm. This article provides an overview of the inherent confusion when new scientific findings confront prevailing medical practice, the history involved in this confusion with respect to FASD, including public policy and legal issues that have arisen around alcohol and pregnancy, and the research and clinical challenges still being faced. Published 2009 Wiley-Liss, Inc.†
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Historically, alcohol has been used for different purposes including as a part of religious observances, as a food, at times as a medicine and its well-known use as a beverage, often in place of uncertain water sources [Vallee 1994, 1998]. It is alcohol's use as a beverage and to some extent as a medicine that have most often come into social and legal conflict, partly as interest in the effects of alcohol on the social fabric of society has waxed and waned and partly due to increasing scientific evidence of alcohol's benefits and risks. While the literature on alcohol's many uses over the millennia is fascinating and growing, we will limit our comments in this article to cyclic waxing and waning of concern for the effects of prenatal alcohol use, primarily focusing on changing views of alcohol's prenatal and antenatal effects.

HISTORICAL REFLECTIONS: WHAT DID WE KNOW AND WHEN DID WE KNOW IT?

As noted by Jones and Smith, "historical reports indicate that the observation of an adverse effect on the fetus of chronic maternal alcoholism is not new" [Jones et al., 1978]. As many authors have concluded, mention of adverse pregnancy outcomes associated with alcohol use have been noted by Aristotle, Plutarch, and Diogenes [Lemoine et al. 2003], in the Bible ([Randall, 2001], in 18th Century England [Warner and Rosett, 1975], and in 19th century medical and temperance literature [Warner and Rosett, 1975]. For example, Aristotle's warning about the effects of drinking on progeny ("foolish, drunken, and harebrained women most often bring forth children like unto themselves, morose, and languid") is often cited as one of the earliest observations of alcohol's effect on pregnancy and pregnancy outcomes. Another often cited reference is Judges 13:7 in which an angel appears to Manoah and his wife and states "Behold, thou shall conceive, and bear a son, and now drink no wine or strong drink . . . ." The couple obeys the admonition and Manoah's wife bears a son, Sampson, who becomes renowned for his physical strength and wisdom. However, much of the literature on alcohol use and pregnancy begins within the 18th century and the "London Gin Epidemic" which is considered by many authors to be the genesis of the first medical warnings about the dire consequences of drinking during pregnancy.

London Gin Epidemic (~1720–1750)

The "London Gin Epidemic" occurred at a time when newer distillation technologies entered England from the Netherlands simultaneous with the ascent of William and Mary (from the same country) to the throne of England. Bans were placed on the importation of French wines, England experienced bumper crops of wheat, and taxes were lowered on gin (distilled from wheat) for the benefit of wealthy landowners. These conditions created what amounted to the "perfect storm" for the production, distribution and consumption of "cheap, plentiful" gin [Warner and Rosett, 1975]. In his often quoted treatise on the excesses of gin drinking as the underlying cause of increased criminal behavior in 18th-century London, the English author and magistrate, Henry

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Fielding, addressed a number of social, moral, and health ills he and other members of the upper social strata attributed to the excess drinking of gin. According to Fielding, "the consumption of [gin] is almost wholly confined to the lowest Order of the People [Fielding, 1751]." Among the ills he described were those inflicted on unborn children and future generations: "... What must become of the Infant who is conceived in Gin? with the poisonous distillations of which it is nourished both in the Womb and the Breast [Fielding, 1751]." Other contemporaries of Fielding made similar observations. For example, customs administrator and noted economist Corbyn Morris observed that the significant death rate relative to births in London was "particularly attributable to the enormous use of spirituous liquors ... which render such as are born meager and sickly and unable to pass through the first stages of life [Morris, 1751]. William Hogarth's depiction of the horrors of gin drinking by the lower classes in his famous Gin Lane [1751] has been described by some authors (but not by all) as depicting the fetal alcohol syndrome [Rodin, 1981; Abel, 2001b].

By 1725 the damage that was attributed to alcohol was so great that the London College of Physicians presented its concerns about the medical and social problems occasioned by excessive alcohol use in a petition to the House of Commons. Among the concerns expressed was that

"... the frequent use of several sorts of distilled Spirituous Liquors ... [is] too often the cause of weak, feeble, distempered children, who must be instead of an advantage and strength, a charge to their Country." Whether prompted by fear of losing the common worker, fear for self and property, or medical concerns about alcohol's effects including those on pregnancy outcome, the observations made by influential Londoners, including Fielding, Morris, and Hogarth, are widely credited as contributing to the eventual repeal of laws that helped fuel the cheap production of gin and the "gin epidemic" [Coffey, 1966].

Not All Agree

Examples of historic knowledge of alcohol's effects on pregnancy such as those described above are presented in many articles on alcohol and pregnancy. The most comprehensive of the earliest reviews of historic observations was an excellent account from ancient times to the early 1970s [Warner and Rosett, 1975]. This article was subsequently criticized in a number of publications [Abel 1997, 1999, 2001a,b; Armstrong and Abel, 2000] for over interpretation and imputing the meaning of historical events to imply that the earlier centuries truly understood alcohol teratogenesis and had seen FAS. For example, while Warner and Rosett suggest that the entry in Judges is a recognition of the harm alcohol can cause during pregnancy, Abel notes that there are other explanations in the biblical text, for example, membership of Manoah in a sect that was abstinent (meaning that Samson should also be abstinent) to account for this admonition without invoking a knowledge of teratology [Abel, 1997]. We would also suggest that it may well have simply reflected an acknowledgement of warnings handed down from antiquity concerning the use of alcohol at the time of conception (by men and women) to prevent damage to the child or to the pregnancy. In this interpretation, both parents were judged capable of damaging a child due to alcohol use. As pointed out by Lemoine, "unfortunately, two errors have persisted throughout time ... very often paternal alcoholism was blamed ..."; and "exaggerations led to accusing alcohol for many unidentified physical and psychological anomalies" [Lemoine, 2003].

That alcohol has an effect on pregnancy outcome is well-documented in 19th and early 20th century literature.

ALCOHOL, MEDICINE, AND POLITICS: TEMPERANCE TO PROHIBITION

"The abuse of alcohol is so mixed up with morals, science, and economics that it is impossible to disentangle the effects of the chemical substance itself from its associated social complexities" [Boycott, 1923].

"Our society's conceptions of disease are often weighted by moral valences as well as biological realities" [Armstrong, 1998].

That alcohol has an effect on pregnancy outcome is well-documented in 19th and early 20th Century literature [Warner and Rosett, 1975]. However, scientific findings were interpreted through the lens of then contemporary public attitudes about alcohol, its linking to a wide variety of social ills by the temperance movement, and by a lack of basic scientific understanding, particularly with regard to the differences between heredity and prenatal effects [Katcher, 1993].

Reviewing 19th century scientific/medical literature, it is difficult to determine whether deficits in children are attributed to alcohol consumption in pregnancy, male and/or female alcohol use at the time of conception or before conception, damage to genetic factors (germ cells); toxic damage to the fetus from alcohol exposure in the womb; alcohol exposure post pregnancy through breast milk, or even the direct feeding of alcohol to the infant in place of breast milk.

One often cited reason for this difficulty is the involvement of a large number of physicians in the temperance movement (primarily in the United States and England) and the subsequent influence of this movement on medical views of alcohol's injurious effects on health in general and on pregnancy outcome in particular.

Another complicating factor with the early literature was a lack of modern (20th century) understanding of genetics, heredity, toxicity, and teratology. In the preMendel period, even knowledgeable physicians were unaware of the heredity principles of Mendelian genetics, and the distinction between genetic inheritance (DNA), damage to the "germ line" (sperm and ova), and direct toxic damage to developing tissues and organs. The Lamarckian view that traits acquired by either parent during his or her lifetime can be passed on to offspring (like inebriety or alcoholism) was not uncommon. Consistent with Lamarck, Robert MacNish of Glasgow wrote in 1835: "the children (of confirmed drunkards) are in general neither numerous nor healthy. From the general defect of vital power in the parental system, they are apt to be puny and emaciated" [MacNish, 1835]. Ironically, we now understand that some aspects of Lamarckian inheritance do indeed exist via mechanisms of epigenetics. This view was somewhat modified by WC Sullivan in his observations on 600 births to female prison inmates. Sullivan found 335 pregnancies ended

in stillbirth or death to surviving children before age 2 and 80 women had three or more such infant deaths. He concluded that although inebriety could be transmitted by either parent to his or her offspring, "maternal inebriety is a condition peculiarly unfavorable to the vitality and to the normal development of the offspring a large part [of which] depends on the primary action of the poison" [Sullivan, 1899].

Between 1912 and 1920 Charles Stockard (Cornell University) conducted what for the time were very careful experiments on pregnancy outcomes in a guinea pig model. Both male and female guinea pigs were exposed to alcohol via an inhalation model before conception. Stockard found effects on growth and viability (liveborn, stillborn) in the offspring. These effects on viability persisted when the 1st generation offspring were mated with guinea pigs without a heritage of alcohol exposure but diminished with each subsequent generation. After four generations, the initial alcohol-exposed line had returned to the values of the control group [Stockard, 1918]. Stockard's findings appear very consistent with the 21st century understanding of epigenetics. MacDowell reproduced Stockard's results with rats finding reduced viability in the first generation and increased litters in the second generation [MacDowell and Vicari 1917; MacDowell, 1922]. He attributed the reduced viability in alcoholized rats to the effect of alcohol on "germplasm bearing factors detrimental to litter production" and "increased litters in the second generation to the elimination of the litters in the first generation that bore the less fertile germinal material" [MacDowell, 1922].

The following passage from an article appearing in the British Journal of Inebriety in 1923 sums up 19th and early 20th century thought on alcohol and pregnancy: "I think it is not an exaggeration to state that alcohol is a poison, and that the fetus of a chronic alcoholic mother is itself a chronic alcoholic, absorbing alcohol from the mother's blood and subsequently from her milk ..." That is, they knew it did damage to the fetus if not exactly how. This knowledge appears to have been widely held among physicians and scientists during this time.

Nascent research progress that had begun during the heyday of early alcohol research came to an abrupt halt in 1919 with the passage of the Volstead Act and the ratification of the 18th Amendment to the US Constitution prohibiting "the manufacture, sale, or transportation of intoxicating liquors ... for beverage purposes" ushering in the era known as Prohibition. From the mid 1850s until Prohibition, many physicians were "temperance" advocates supporting total abstinence from alcohol use [Varma and Sharma, 1981]. By the time Prohibition became a reality, public opinion, largely stimulated by the temperance movement, had shifted from a view of inebriety as being an individual problem to one that found alcohol at the root of most health and social ills. With alcohol ostensibly no longer available, problems related to its use were viewed as less urgent. When Prohibition ended in the United States in 1933, temperance leaders and temperance tenets were by and large denounced. The country had swung away from the view of alcohol as villain to one that viewed alcoholism, rather than alcohol use, as the problem. A new era in alcohol science resulted, in which alcohol's harmful effects were minimized, and the study of alcoholism (once again an individual problem) became the prime scientific/medical focus [Katcher, 1993].

ALCOHOL AND PREGNANCY RESEARCH: POSTPROHIBITION AND BEYOND

A clear cycle can be seen between the large attention to drinking during pregnancy that occurred during the late 19th and early 20th centuries, to the "forgetfulness" of the harmful consequences of alcohol use [Warner and Rosett, 1975]. The country that had seen Prohibition turn into one of the deadliest crime waves then known, wanted nothing to do with alcohol as a problem. Not only did the country repudiate the prohibition of alcohol, but also the large body of science that had been generated during the late 19th and early 20th centuries likely because much of it was associated with temperance movement "moralism." Many of the physicians and scientists who had been involved in generating much of this science were so integrally identified with the temperance movement that most of their research was dismissed as reflecting a no longer fashionable "moral" view of alcohol [Katcher, 1993]. This carried over in the 1940s as scientists began, once more, to address concerns about harmful alcohol use [Warner and Rosett, 1975]. These scientists made it perfectly clear that their problem was not with alcohol use in the main, but in what has come to be known as chronic late stage alcohol dependence. In an interesting chapter-by-chapter repudiation of late 19th early 20th century temperance "science" on alcohol, Haggard and Jellinek sought to distance the neo-science of "chronic intolerance" (alcoholism) from the temperance-colored science published in the earlier century. They wanted the focus on alcoholism, not on alcohol. Writing in a 1942 book covering what was then known about the biological and psychological effects of alcohol, Haggard and Jellinek addressed the temperance view of alcohol's damage to the "germ" or the egg of the mother and/or sperm of the father, thus affecting the physical/mental status of the child. According to Haggard and Jellinek, ascribing damage to the child as a result of drinking alcohol was a "belief, reflected in myth and custom ..." that has "maintained itself up to present times." Thus, they approached alcohol not in terms of alcohol as a teratogen, but of alcohol's effect on reproduction and associated organs. While acknowledging that the appearance of feeblemindedness, epilepsy and mental disorders are more frequent among the offspring of abnormal drinkers, they stated unequivocally that this was not a direct effect of alcohol, but of "bad stock" or defects inherited by offspring "which predispose to alcoholism" [Haggard and Jellinek, 1942].

Even then, vestiges of the country's dislike of the temperance movement and Prohibition remained and Jellinek, often referenced as the father of the modern era of alcoholism research, and others who were at the head of alcohol's rediscovery as a researchable topic, did not believe that maternal alcohol use was detrimental to the fetus. In fact, Haggard and Jellinek wrote, "the fact is that no acceptable evidence has ever been offered to show that acute alcoholic intoxication has any effect whatsoever on the human germ or ... in altering heredity" [Warner and Rosett, 1975]. They posited that the damaged children of alcoholic parents were the result of poor nutrition; alcohol exposure in the womb as the agent responsible for causing physical and mental abnormalities in children did not appear to be a possibility.

Modern Recognition of Alcohol as a Teratogen

We now know that alcohol, certainly when consumed at doses consist-

ent with the lowest thresholds of legal intoxication (0.08% blood alcohol concentration) is an agent capable of causing not only a variety of health problems but also capable of causing birth defects. Alcohol is a teratogen. Because of its common availability and usage, alcohol is more than just a teratogen; it is the most prominent behavioral teratogen in the world. Indeed, alcohol may be viewed as having introduced an entirely new discipline—that of behavioral teratology.

FAS as a Modern Diagnosis

In 1970, Christine Ulleland, a medical student at the University of Washington, undertook a thesis project to study children hospitalized for failure to thrive. In reviewing the medical charts, she observed that a common element in the medical records was an indication of alcoholism in over 41% of the mothers noting, "these observations indicate that infants of alcoholic mothers are at high risk for pre- and postnatal growth and developmental failure," and suggesting that "greater attention should be given to alcoholic women during the child bearing years" [Ulleland, 1970].

When the prominent dysmorphologist David Smith, and his associate, Kenneth Lyons Jones examined a group of these children they immediately recognized the subtle, but important pattern we now know as FAS. The physical and behavioral characteristics of these children were subsequently published [Jones et al., 1973], ushering in the modern era of research on fetal alcohol syndrome.

In their search for other evidence of the adverse effects of alcohol on fetal outcome, Jones and Smith discovered a paper published in 1968 in France, by Lemoine et al., [1968] describing virtually the identical physical and behavioral problems among 127 children of alcoholic mothers from Roubaix, France. The Lemoine paper had likely escaped attention because it appeared in a minor journal and was published in French [Warner and Rosett, 1975]. Subsequently, an earlier doctoral dissertation on the influence of parental alcoholic intoxication on the physical development of young babies by Jacqueline Rouquette, published in Paris in 1957, came to the attention of FAS researchers [Barrison et al., 1985]. In their second publication, David Smith introduced the name "fetal alcohol syndrome" to describe their clinical observations [Jones and Smith, 1973]. It was often the case that a new syndrome would be named for the scientists or physicians who first describe the condition (e.g., Williams's Syndrome). The authors chose to assign the name fetal alcohol syndrome (FAS) because they believed that the name would call attention to alcohol as a teratogen, alert women to the dangers of drinking in pregnancy and aid in the elimination of this disorder. While the name FAS does garner attention in the medical community and public, some argue that the name FAS today may actually be more problematic due to the stigma associated with alcohol problems than if a neutral name like "Smith and Jones" or "Lemoine" syndrome had been applied.

No Immediate Acceptance

Despite the Lemoine and Jones and Smith reports, much skepticism as to whether alcohol could cause birth defects existed in the 1970s. For example, if it truly existed, why did we not know about it before in this era of modern medicine? How did we know that alcohol was indeed the agent rather than nutrition, other drug use, or the "deviant lifestyle" of the alcoholic woman?

Because of its common availability and usage, alcohol is more than just a teratogen; it is the most prominent behavioral teratogen in the world.

The answer to these questions required the undertaking of animal and epidemiological research and a funding agency to support that research.

The National Institute on Alcohol Abuse and Alcoholism and FAS: The Story of a Science Success

In the late 1960s, a United States Senator, Harold E. Hughes, himself a recovering alcoholic, along with a group of influential recovering alcoholics with business and political acumen and ties, began advocating for legislation to create a federal focal point for alcoholism. At this time, medicine had little if any concern for alcoholics who were seen as morally deficient, or suffering from weak wills or character defects (shades of the earlier 19th/20th centuries temperance movement). Treatment for alcoholism was mainly accomplished through Alcoholics Anonymous, and to a much smaller extent within state mental health systems (a small center for the control and prevention of alcoholism in the National Institute of Mental Health was tasked with helping to create a federal alcoholism presence mainly within the existing federal and state mental health services system).

Many early alcohol investigators noted that alcohol research was as stigmatized as alcoholism itself [Lieber, 1988]. The National Institutes of Health supported very limited alcohol research; what was supported was often disguised as something else, e.g., using alcohol as a "probe" to study other types of liver disease. Indeed, a major epidemiological study of birth defects undertaken in the late 1960s did not ask any questions on alcohol use [Jones et al., 1974]. This attitude changed with the passage of the landmark Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment and Rehabilitation Act of 1970 (P.L. 91-616) which established the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and provided national visibility and funds to understand, prevent, and treat alcoholism and problems related to alcoholism. NIAAA, with its newly minted research mandate, supported the research that helped to validate the existence of FAS and what we now recognize as the full spectrum of fetal alcohol spectrum disorders (FASD).

The 1970s alcohol and pregnancy research took two forms: animal research and human epidemiological research. Animal research established the nature of FAS teratogenesis by verifying that the same deficits reported by Lemoine and Jones and Smith could be seen in animals (rodents, dogs, and later primates); and that alcohol and not other confounding factors were responsible. Human epidemiological research prospectively examining the outcomes of children exposed to alcohol in pregnancy demonstrated the range of physical and behavioral deficits in children exposed to alcohol in pregnancy. By 1977, NIAAA sponsored the first international research conference on FAS. Though not an original intent of the meeting, those attending were so impressed with the findings to date that they collectively recommended that

NIAAA issue the first government health advisory on FAS.

Warning the Public

Doing anything the first time in Government presents numerous challenges. In this instance, NIAAA was attempting to have the Federal Government put its imprimatur on a warning about drinking during pregnancy that ran counter to prevailing medical and social practices. Resistance from within the US Department of Health, Education and Welfare (now the US Department of Health and Human Services), NIAAA's administrative home, and from non-Federal groups and organizations was expected. Federal skepticism was overcome primarily due to the strength of the science, and the first governmental advisory about alcohol use during pregnancy was published by NIAAA in 1977 [Warren and Foudin, 2001]. Taking a "conservative approach" this first ever advisory stated that more than six drinks a day was dangerous and recommended a "2-Drink Limit" per day. Unlike today's warnings against any use until proven safe, implicit in this first warning was the notion that alcohol use is "safe" within the given guidelines until proven dangerous.

The response was as varied (and as vocal) as expected. For example, the recommendation in the advisory was supported by the American College of Pediatrics, but not immediately by the American College of Obstetrics and Gynecology. Some medical and patient advocacy organizations criticized NIAAA for going too far, and some for not going far enough, by not recommending abstinence during pregnancy. However, the 1977 Health Advisory did focus sufficient attention on the issue of alcohol and pregnancy that Senate hearings were held for the purpose of considering legislation requiring warning labels related to alcohol and pregnancy risks. The outcome of the hearings was the call for a Report to the President and Congress on *Health Hazards Associated with Alcohol and Methods to Inform the General Public of these Hazards* prepared jointly by the Departments of Health and Human Services and Treasury (US Department of Transportation and US Department of Health and Human Services, 1980]. The report did not immediately call for alcoholic beverage labeling but did recommend the issuance of a Surgeon General's Advisory on Alcohol and Pregnancy that was subsequently issued in 1981 (FDA Drug Bulletin 1981]. Unlike the previous Advisory, the 1981 Advisory recommended that women who are pregnant or planning to become pregnant avoid alcohol. In 1988 Congress considered the issue of alcoholic beverage labeling as a means to warn of the dangers of alcohol exposure in the womb and enacted the Alcoholic Beverage Labeling Act of 1988 (Public Law 100-690) which became effective in 1989. In 2005, the Surgeon General reissued an updated advisory on alcohol use and pregnancy that warned against FASD, the full spectrum of birth defects caused by prenatal alcohol exposure (US Surgeon General, 2005]

CONCLUSION: PROMISES OF CURRENT RESEARCH

Although today there is little disagreement about the existence of FASD, we are again embroiled in determinations that are as much about policy as medicine. What does a physician tell his/her patient who is either pregnant or may become pregnant? The US Surgeon General's Advisory on Alcohol and Pregnancy is clear. We do not know the dose at which we can unequivocally state that the fetus will not be harmed. It is therefore prudent advice to avoid all drinking during these time periods. Yet, there is not full agreement on this issue. Recently, for example, a medical ethicist likened this message to "medical paternalism" [Gavaghan, 2009]. As science continues to refine our knowledge of the consequences of exposure to alcohol during gestation, we are hopeful that public health policies and practice can reach closure on what advice will best serve pregnant women and their future offspring.

As concluded by Clarren and Smith, alcohol exposure during gestation "appears to be the most frequent known teratogenic cause of mental deficiency in the Western world" which "through accurate understanding . . . and widespread public awareness could be largely reduced and, ideally, eliminated" [Clarren and Smith, 1978]. This was the goal of the early pioneers in describing FAS and FASD, and it remains the goal of committed scientists, patients, and their families today. ■

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