Review Article

Integrative Diabetes and Cardiovascular Diseases

Fetal Alcohol Spectrum Disorder: Risk for Diabetes and Congenital Heart Defects

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Abstract

Excessive use of alcohol can be a cause for many disease and injury conditions. These include amongst many others, myocardial infarction, diabetes mellitus, atrial fibrillation, nonischaemic cardiomyopathy, fetal alcohol spectrum disorder (FASD), congenital heart defects (CHD) and liver cirrhosis. Even low levels of prenatal alcohol (ethanol) exposure, such as in a single dose, can produce birth defects termed fetal alcohol syndrome (FAS) which is the highest marker on the spectrum. Diabetes is regarded as a major cause of cardiovascular disease whilst prenatal alcohol exposure (PAE) can range from no observable adverse effects to mortality. CHD are stated to be the most prevalent cause of mortality in individuals with FASD. The dimension of the problems is still greatest in the Western world although it is stated to be the leading cause of mental retardation in North America. FASD is a neurodevelopmental disability which can be occasioned when a pregnant woman consumes alcohol. The diagnostic criteria for FASD includes growth impairment, abnormal facial features and neurocognitive impairments. The most frequently reported abnormal facial features in FASD are thin upper lip, indistinct or smooth philtrum and short palpebral fissure length. Other features are microganthia, low set ears, ptosis, absent or indistinct philtral ridge, epicanthal folds, cleft palate, flat nasal bridge and midface hypoplasia. The neurocognitive features commonly reported in FASD are microcephaly, intellectual disability, attention-deficit hyperactivity disorder (ADHD) and behavioural impairments. Central nervous system (CNS) injury is also seen and is debilitating. Structural abnormalities of the CNS can include microcephaly, agenesis/absence of the corpus callosum and multiple severe brain malformations. This review article seeks to address the association of FASD with diabetes and CHD.

Keywords: Fetal alcohol spectrum disorder; Fetal alcohol syndrome; Congenital heart defects; Diabetes; Prenatal alcohol exposure

Abbreviations: IGF: Insulin-like Growth Factor; GLUT4: Insulin-regulated Glucose Transporter Found Primarily in Adipose Tissues and Striated Muscle (skeletal and cardiac); ObR: leptin Receptor; mRNA: Messenger Ribonucleic Acid; ADHD: Attention-deficit Hyperactivity Disorder

Introduction

The range of structural abnormalities and functional deficits caused by PAE are referred to as FASD. Alcohol's teratogenic effects are said to have a lifelong impact and affects the individual's daily living and general health, lower immune function, glucose intolerance and hyperinsulemia [1]. Glucose homeostasis may also be impaired in adults with PAE which may influence risk for diabetes. PAE may increase insulin resistance...
and glucose intolerance, both of which are factors in the pathophysiology of type-2 diabetes. De la Monte et al. purport that PAE is associated with hypoplasia and impaired neuronal migration in the cerebellum. Neuronal survival and motility are stimulated by insulin and insulin-like growth factor (IGF) whose signalling pathways are major targets of ethanol neurotoxicity. Gestational exposure to alcohol may produce hypertriglyceridaemia[2]. Elevated triglycerides increase the risk for cardiovascular disease, acute pancreatitis and CHD [3]. CHDs refer to the structural anomalies of the heart and great vessels that are present at birth and can disrupt the normal flow of blood through the heart or vessels near it.

Although there are inconsistent conclusions about the association of prenatal alcohol drinking with diabetes and CHDs, Burd et al. purported that the potential magnitude of the relationship between PAE and CHD may be substantial although the rate of comorbidity has not been systematically examined. They consequently utilized a systematic review of published literature on the comorbidity of CHD and FASD [4]. The utilized nomenclature for the continuum of adverse effects consisted of four categorical syndromes encompassed under the term FASD. A diagnosis of FAS requires growth impairment usually below the 10th percentile for height and weight, neurocognitive delays and/or mental disorders (mental retardation, attention-deficit hyperactivity or developmental delays) and at least two characteristic facial features (short palpebral fissures <10th, thin vermilion border or smooth philtrum) and PAE [5]. Retrospectively, the three other diagnostic categories were partial FAS (pFAS) (where one of the criteria for a diagnosis of FAS is absent), alcohol-related neurodevelopmental disorder (ARND) and alcohol-related birth defects (ARBD) [4]. These diagnoses are still in current usage. The diagnoses require that the abnormalities are relative to PAE. FASD is thought to be intergenerational with societal implications being substantial, as is the cost of care.

Burd et al. argued that the mortality rates of FASD ranged from 4% to 5%, the mortality rates for siblings of FASD are increased 530% and the maternal mortality rate over a 10 year period is about 4.5%. The difficulty of identification of FASD in very low birth weight infants and in infants with multiple birth defects may be an important source of ascertainment bias in the estimation of comorbidity rates for CHD and FASD [4]. CHD may also result from alcohol exposure combined with one or more adverse risk factors such as diabetes, maternal smoking, and poor diet [4].

**History**

The first mention of alcohol as a component of diet and communal events dates back to the 7th millennium BC. Famous ancient savants such as Hippocrates used alcohol as a solvent for herb extracts, as an antiseptic and to counteract lethargy and diarrhoea, whereas in medieval times alcohol was well within the armamentarium of anaesthetics, sedatives, disinfectants and diuretics [6]. Of note is the fact that the Holy Bible in Judges 13:7 states “Behold thou shalt conceive and bear a son: and now drink no wine or strong drink” hinting at the problems associated with alcohol and pregnancy. In Carthage, there was reported to be a prohibition against couples drinking on their wedding night to prevent producing an affected offspring. Aristotle, the founder of Western thought, even proclaimed “Foolish, drunken and hare-brained women most often bring forth children like unto themselves, morose and languid” [7, 10]. Interestingly, the dispute surrounding the optimal quantity of alcohol that should be consumed has a history almost as long as the history of alcohol itself. The Greek poet Eubulus (375BC) voted for 3 Kylix cups (=250 mL) and in one of his plays had Dionysus, the God of Wine, say “Three bowls do I mix for the temperate: one to health, which they empty first, the second to love and pleasure, the third to sleep. When this bowl is drunk up, wise guests go home.” [6]. Because it was customary at that time to dilute wine in a ratio of 1:2 or 1:3, Eubulus’s view comes close to current guidelines. However, all of the recommendations suffer from the fact that the thresholds of healthy moderation are population averages and do not necessarily reflect correct individual thresholds. Actually, intestinal degradation, absorption, metabolism and blood clearance of ethanol are all subject to high inter-individual variability [6]. Notably, The World Health Organization states that in 2010 the world-wide average amount of pure alcohol consumed per person aged ≥15 years was 6.2 L/y or 13.5 g/d [8].

Nowadays, of course, alcohol is no longer administered for medicinal purposes, but it is a frequent constituent of regular diet, favoured for its broad availability and lack of effective sale restrictions [6]. It is also argued that alcohol in moderation favourably affects reverse cholesterol transport, insulin sensitivity, abdominal obesity, systemic inflammation and oxidative stress, endothelial function, endogenous fibrinolysis, post-prandial hypercoaguability and platelet aggregation [6].

Importantly, there is now solid evidence that alcohol, when consumed regularly and at low volumes (up to one drink for women and two drinks for men on a daily
environment can have long lasting deleterious effects

The Public Health Issue

It is well recognised that an adverse intrauterine environment can have long lasting deleterious effects on an individual's health status. One clinical marker for an adverse intrauterine environment is low birth weight, a result of decreased fetal growth, which has been associated with characteristics of the metabolic syndrome including impaired glucose tolerance, insulin resistance and type-2 diabetes in adult life [14]. Poorer immunity, glucose intolerance and hyperinsulemia have also been reported [1] as mentioned earlier [15].

In 2002 as many as 7 per 1000 women were binge drinking during pregnancy and even higher percentages consumed alcohol at various times during pregnancy[15]. Binge drinking has not declined among women of childbearing age in the USA and New Zealand [15, 10]. FASD is not one entity – rather a collection of heterogeneous disorders that range broadly in terms of severity and outcomes [16]. FAS is the most severe form of FASD and is associated with intrauterine growth restriction, CNS malformations, mental retardation and craniofacial and skeletal defects whereas less severe effects of PAE are classified as ARBD, pFAS and ARND [17] (See above).

The economic burden of FASD/FAS is high [18, 10] and despite public health efforts worldwide, the incidence rates have not declined over time [10]. The annual cost of care in the US in 2007 was estimated to be $3.6 billion and the lifetime cost of care per individual was $2.9 million [4]. There is no specific report available estimating such costs in the US today. Addressing research relative to CHD and FASD, Burd et al. conducted a database search to identify papers reporting the prevalence of the association. Of the 29 studies which met their inclusion criteria, there were 12 case series studies of subjects with FASD. They found that the proportion of cases with a CHD (atrial [ASD] and ventricular [VSD] septal defects, other defects or unspecified CHD) ranged from 33% to 100%. From 14 retrospective studies, the rate of septal defects was 21%, other structural defects 6% and unspecified defects was 12%. For 2 case-control studies, the odds of CHD ranged from 1.0 (subjects with fetal alcohol effects [FAE] – an old term) to 18.0 (subjects with FAS). In the one prospective study of CHD the odds ratio for a child to have CHD and FASD was 1.0 [4].

Epidemiologic data indicate that in the US, FAS rates range from 0.2-1.5 per 1,000 live births, whereas ARBD and ARND disorders occur in approximately 0.9% of live births [5]. These are estimates only [10]. Increased tendency of adolescents and young people to participate in high-risk behaviours, including the abuse of alcohol during pregnancy is thought to be mediated by structural
and functional CNS abnormalities, but could also be consequential to heavy chronic or binge alcohol abuse during adolescence. In essence, alcohol abuse in adolescence and young adults establishes a vicious cycle whereby impaired judgement and cognition increase the risk of causing PAE. Thus, the long-term consequences of PAE range from behavioural abnormalities to learning disabilities, ADHD to mental retardation [19, 20] and FASD [10].

**Mortality and Fetal Alcohol Spectrum Disorder**

The context of PAE and a diagnosis of FASD can offer important information on a variety of multifaceted and interacting risk markers and increase our understanding of the risk for mortality and adverse outcomes. CHDs are common birth defects with highly variable severity [4]. In the US over 35,000 new cases of CHD are born each year (about 1% of infants have a CHD) and one million people live with CHD [21]. The incidence of CHD ranges from 4 per 1000-50 per 1000 live births [21]. The structural deficits associated with PAE and mortality are large and include effects from exposure over multiple embryonic periods of development likely in concert with other modifiers of exposure. Important, non-lethal abnormalities are likely to have implications for subsequent neurobehavioural development and risk for mental disorders. These risks will likely change over time in response to past development and both age and development dependent demands. The potential range of neurobehavioural deficits seems large and in contrast to the typical facial features of FAS, many will have significant developmental implications far into the future as neurobehavioural development continues [22].

World-wide alcohol abuse now accounts for 4% of total world-wide mortality and between 4% and 5% of all disability-adjusted life years [21]. The prevalence of drinking during pregnancy is quite high especially prior to pregnancy recognition when slightly more than 50% of women in the United States report some alcohol use [22]. Many pregnancies are unplanned making early exposure common [10]. The prevalence of alcohol exposure decreases from 50% prior to pregnancy recognition to around 10% upon recognition of pregnancy. About 3%-5% of women continue to drink throughout pregnancy and many drink heavily, more than five drinks per occasion and often several times per week [20, 10]. Thus, several hundred thousand pregnancies have PAE exposure at levels increasing risk for FASD. Whilst PAE can result in damage to any of the organ systems, the heart and brain appear to be the two most commonly reported organ systems [20]. However, recently Patel et al. have reported that they found no increase in risk for non-syndromic atrioventricular septal defects attributable to maternal alcohol consumption in a large data set from the National Birth Defects Prevention Study [22].

Case study reviews undertaken by Thompson et al. relating to FASD and mortality indicate that there is an early age of death distribution which they found surprising given that a diagnosis of FASD is difficult in infancy and early childhood [20]. In fact, a diagnosis of FASD is often delayed until middle childhood and mortality rates in FASD are increased [23]. Given the prevalence at about 1% of live births [10] case reports and case series studies of mortality should be common rather than to 57 cases which were found by them. It therefore, seems likely that most cases of mortality in FASD occur in a context where FASD (likely even the potential role of PAE) is not routinely considered [4]. It has previously been suggested that a context of PAE should be considered in all infant and childhood deaths [4] given the fact that a diagnosis of FASD is associated with an increased risk of death for affected people and their siblings (even when the sibling FASD status is unknown [23]. In populations of children with FASD recent reports suggest a 5%-6% mortality risk [23, 24]. Several reports have also demonstrated increased rates of mortality in mothers of children with FASD [25].

**Diabetes and Fetal Alcohol Spectrum Disorder**

In the last few decades it has become increasingly evident that PAE may also alter glucose homeostasis and increase the risk of type-2 diabetes [3]. Indeed, and as reported earlier, glucose intolerance and hyperinsulinaemia have been found in children born with FAS [1]. In the fasted adult, alcohol has been shown to induce hypoglycaemia through the interference of gluconeogenesis but with little effect on glycogenolysis [14]. Similarly, adult rats chronically fed alcohol develop hypoglycaemia, also due to decreased gluconeogenesis, with females being more severely affected than males [15] (Leong et al. would argue otherwise). In rats, fetal alcohol exposure has been shown to induce hypoglycaemia in late gestation as well as in early postnatal life [15]. However, unlike the adult, this fetal hypoglycaemia is associated with decreased hepatic glycogen stores and not decreased gluconeogenesis, as gluconeogenesis does not occur during fetal life for either rats or humans [14].
As acknowledged, low birth weight in humans predisposes to obesity, cardiovascular diseases and type-2 diabetes in adult life [3]. Alcohol exposure during pregnancy has been associated with fetal growth restriction [3]. Other researchers, namely Chen and Nyomba investigated the effects of prenatal exposure to alcohol on glucose metabolism later in the offspring [3]. They gave female Sprague-Dawley ratsethanol, 4g/kg/day by gavage throughout pregnancy. Compared with controls, new born ‘ethanol’ rats had decreased body size (5.1 ± 0.1 v 6.3 ± 0.1g, P<.001), plasma insulin (0.44 ± 0.4 v 0.67 ± 0.1 ng/mL, P<.05), and leptin mRNA (P<.05), but they had normal β-cell mass and elevated adipose resistin mRNA and plasma glucose (5.0 ± 0.5 v 3.6 ± 0.3 mmol/L, P<.01). Food intake was decreased in ‘alcohol’ rats during the fourth week of life and body weight remained decreased compared with controls until a catch-up growth occurred by seven weeks of life. At 13 weeks of age, body weight and β-cell mass of ‘ethanol’ offspring were normal, but plasma glucose and insulin after a glucose challenge were increased compared with controls (P<.05). Adipose leptin and hypothalamic Ob-R mRNA were not different from controls, but resistin was increased (P<.05) and muscle GLUT4 content was decreased (P<.05) in ‘alcohol’ offspring compared with controls. Thus, the data suggest that PAE impairs glucose tolerance in the offspring by both inducing insulin resistance and β-cell dysfunction. The prevailing mechanism in 3-month-old rat offspring appears to be insulin resistance (confirming and supporting reported earlier work), manifested by glucose intolerance and decreased GLUT4 despite hyperinsulinemia [3].

Congenital Heart Defects and Fetal Alcohol Spectrum Disorder

PAE is routinely accompanied by high rates of maternal smoking, poor diet, other substance abuse and multiple other adverse factors which increase the risk for a broad range of adverse outcomes in exposed pregnancies including CHD [4]. Thus, it can be said that an unknown number of CHD in these individuals would be attributed to factors other than PAE. CHD may also result from alcohol exposure combined with diabetes [4].

The study undertaken in the United States in 2013 and reported earlier, identified 57 deaths occurring in individuals with FASD and a potential cause of death for 49 (86%) [20]. It reported that the most common cause of death in individuals with FASD was CHD 37/49 (75.5%) with suspected or confirmed CHD including atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, hypoplastic left heart, aortic arch interruption, etc. However, for some cases (58% male; 42% female) it was difficult to determine if the heart defect was the cause of death, a complicating condition or related post-mortem finding [21]. Also, the limitations of this study indicated that the nomenclature for diagnosis had been modified over the past 35 years for cases included in the review, that there is no widely accepted threshold for exposure that is necessary or sufficient to cause FASD and it is likely that many deaths occur in people with undiagnosed FASD or where a past diagnosis is not available at the time of the death [20].

In the US alone, there are 40,000 new cases of FASD each year and in the population birth through to 18 years of age, about 720,000 people have FASD. In this population several hundred deaths would be expected each year. This suggests that most cases of FASD are missed in mortality reviews [20]. Karunamuni et al. on this issue purport that as high as 54% of live-born children with FAS present with cardiac anomalies e.g. valvuloseptal defects and pulmonary stenosis [26] that can lead to developmental challenges and on-going medical care.

The mechanisms of alcohol-induced CHD remain largely unclear even though its etiology has been the focus of much study, especially the cellular and molecular mechanisms. One aspect that has not been thoroughly investigated owing to technological limitations is the role of abnormal cardiac function in the progression of FASD-related CHDs [26]. The few studies that have measured cardiac function in FASD animal models support the
hypothesis that CHDs arising from ethanol exposure could have a significant contribution from abnormal function [26]. Abnormal embryonic cardiac function (as well as abnormal valves) was identified through ultrasound and histology, respectively at late stages (embryonic day 15.5) [italics researchers] of mouse development after ethanol exposure at gastrulation [27,28]. Functional and structural defects, including anomalies in heart volume/morphology and conduction, were observed in late-stage zebrafish after ethanol exposure, thus mimicking malformations occurring in patients with FASD [29].

Discussion

Many previous studies have focused on the neurodevelopmental symptoms of FASD, but comparatively few have investigated cardiac birth defects and diabetes associated with PAE. Those found have been addressed as above and are now discussed.

So from the data reported, it is well established that chronic heavy ethanol exposure in adult humans is a significant risk factor for symptoms of metabolic syndrome, including impaired glucose homeostasis, diabetes mellitus, hypertriglyceridemia, CHD, abdominal obesity, high blood pressure, cirrhosis, atrial fibrillation and FASD. Children with FASD have hyperinsulinemia and hyperglycemia in oral glucose tolerance tests compared with typically developing children suggesting that the former children are insulin resistant (cf Chen & Nyomba [3]).

To recapitulate, FASD is a developmental disorder that manifests through a range of cognitive, adaptive, physiological and neurobiological deficits resulting from PAE in utero. The disability has proven difficult to identify in the absence of the overt physical features characteristic of FAS. As interventions may have the greatest impact at an early age, Salmon postulates that accurate biomarkers are needed to identify children at risk for FASD. Consequently, DNA methylation signature is being used to develop a possible epigenetic predictor of FASD [10, 27]. However, despite the fact that alcohol was identified as a teratogen many decades ago, recent data indicate that in the US over 500,000 women per year report drinking during pregnancy with one in five of this population admitting to binge drinking [27]. Salmon also reports binge drinking by many of the women in her NZ study, some of whom were not aware that they were pregnant at the time [10]. Acknowledging the latter point and supporting Salmon's statement, Karunamuni et al. study established a quail model of FAS that mimicked a binge-drinking exposure at the stage of gastrulation, at which point a woman may not yet be aware of her pregnancy [26].

The severity of the cardiac defects associated with acute ethanol exposure has previously been shown to vary depending on dosage and timing of the exposure [30]. Also, clinical trials have already demonstrated that ethanol exposure can have direct vascular effects, including basal vasoconstriction and potentiation of vasodilation [31].

One possible rescue strategy could involve the use of pharmaceutical drugs to directly modulate cardiovascular function to reduce, if not block, the progression of ethanol-induced CHDs. This could be a first step in implementing new therapeutic strategies based on the early and accurate diagnosis of cardiac birth defects in FASD.

Conclusion

From the foregoing, it remains unclear as to whether the heart is the primary site of action for ethanol or whether the cardiac anomalies are secondary effects induced by another target [26]. Moreover, there are still inconsistent conclusions about the association of PAE with CHDs, which are the most common group of birth defects and have great public health significance.

Importantly, there could be methodological limitations to the studies discussed which could account for the inconsistencies e.g. misclassification of alcohol intake, under-reporting, no precise volume of alcohol consumption considered, lack of statistical power; alcohol concentrations among types of alcohol used may also influence the accurate classification of alcohol use between groups.

Fundamentally, the findings from Burd et al. review support increased attention from paediatric pathologists, obstetricians and perinatologists of PAE as an etiology for CHD [4]. Routine screening for PAE by such health professionals including cardiologist's evaluation of individuals with CHD would improve on the potential role of PAE in mortality, especially in still births and in premature infants with CHD. It would also improve our understanding of the role PAE plays in CHD as well as increasing our understanding of both cardiac phenotype(s) and prevalence of CHD. This surveillance could also potentially impact the number of recurrent cases of FASD which may be as high as 75% if the mother...
continues to abuse alcohol in subsequent pregnancies [4].

It is noted that low-moderate chronic PAE has subtle, sex specific effects on glucose homeostasis in the young adult rate with males being more severely affected [14]. As aging is associated with glucose dysregulation, further studies addressing FASD will clarify the long-lasting effects of PAE which may increase insulin resistance and glucose intolerance – both factors associated with the pathophysiology of type-2 diabetes. Furthermore, other studies are still required to investigate the association of FASD with CHDs and diabetes.

In vino veritas stated the Greek lyric poet Alkaios of Mytilene (630BC) with others adding “In aqua sanitas”.

References


