Mini Review

Review shows that early fetal alcohol exposure may cause adverse effects even when the mother consumes low levels

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Short title: Effects of fetal alcohol exposure

Abstract

Aim: Studies are increasingly focusing on the effects of prenatal alcohol exposure (PAE) on child health. The aim of this review was to provide paediatricians with new insights to help them communicate key messages about avoiding alcohol during pregnancy.

Methods: Inspired by the 7th International Conference on Fetal Alcohol Spectrum Disorder, which focused on integrating research, policy and practice, we studied English language papers published since 2010 on how early PAE triggered epigenetic mechanisms that had an impact on the development of some chronic diseases. We also report the findings of a human study using three-dimensional photography of the face to explore associations between PAE and craniofacial phenotyping.
Results: Animal models with different alcohol exposure patterns show that early PAE may lead to long-term chronic effects, due to developmental programming for some adult diseases in cardiovascular, metabolic and renal systems. The study with threedimensional photograping is very promising in helping paediatricians to understand how even small amounts of PAE can affect craniofacial phenotyping.

Conclusion: Even low levels of PAE can cause adverse fetal effects and not just in the brain. It is not currently possible to determine a safe period and level when alcohol consumption won’t affect the fetus.

Key words: Alcohol during pregnancy, Epigenetics, Fetal alcohol syndrome, Fetal programming, Teratogenicity

Key notes
- This review provides paediatricians with new insights into the effects of prenatal alcohol exposure (PAE) to help them communicate key messages about avoiding alcohol during pregnancy.
- We looked at studies published in English since 2010, which show that even low levels of PAE can cause adverse fetal effects.
- It is not currently possible to determine a safe period and level when alcohol consumption won’t affect the fetus.

INTRODUCTION
The comprehensive description of clinical patterns of birth defects in children exposed to alcohol during fetal life was coined by two American pediatricians for the first time in 1973, when they used the term fetal alcohol syndrome (FAS) (1). Their work probably
boosted the intensive research that has been carried out since then to understand the mechanisms of injuries caused by prenatal alcohol exposure (PAE). Prenatal alcohol is now regarded as a teratogen, due to its potential to cause malformations in the womb. Our knowledge has increased further thanks to the progress made in new research fields, including epigenetics, and advanced digital imaging techniques. The basic phenotype of FAS comprises growth deficiencies, facial dysmorphological traits and damage to the developing brain (Figure 1 and 2). Varying incidence rates of other defects from different organs may also be present.

FAS is one of the most severe conditions to occur when alcohol exposure is high and, or, recurrent during the susceptible period of fetal development in the first trimester of pregnancy. But research carried out over the last decades has indicated that even small quantities of alcohol exposure may lead to adverse effects on brain development, without infants displaying visible structural deficiencies (2). This condition is entitled fetal alcohol spectrum disorders (FASD) and the main outcomes are that the child can experience problems with regard to their neurocognitive, learning and adaptive functions. The majority of cases of fetal exposure may not have evident facial features. Children who have substantial deficiencies are easier to recognise than ones with less obvious defects. However, many parents claim there are different barriers with regard to physicians’ knowledge, the amount of time it takes to detect issues, the procedure for diagnosis and the rehabilitation facilities that are available (3).

**Epidemiology of PAE and FAS**

Understanding the magnitude of prenatal alcohol exposure is a prerequisite when the key aim is detecting affected children. A systematic review and meta-analysis published in 2017 provided global population-based prevalence data for drinking alcohol during
pregnancy and estimates of FAS. It stated that approximately 10% of women in the general population worldwide consumed alcohol during pregnancy and one in 67 gave birth to a child with FAS (4). In 2007, figures presented at the 7th International conference on FASD research stated that the prevalence of FAS and FASD in the USA were 0.4% and 4.8% respectively (5). These estimates vary in different countries, depending on the specific traditions and strategies that exist in societies. For example, while the amount of women who use alcohol during pregnancy in Sweden is 6-12% (6,7) the prevalence is much higher in neighbouring countries, such as Denmark (46%), and in the United Kingdom (41%) (4). More detailed mapping of fetal alcohol exposure during pregnancy reveals that the figures for alcohol intake are more substantial in the periconceptional period, with higher risks for the fetus. A 2017 study reported that 60% of women drank alcohol before they realised they were pregnant and binge drinking was more prevalent (8).

The extent of fetal exposure may be better understood by explaining how fast alcohol is transferred to the fetus through the placenta and that within a few hours the levels in the fetus and mother are equal. In addition, the alcohol remains in the fetus for much longer, because its ability to metabolise ethanol is only 5-10% of the mother's capacity (9). The factors leading to negative effects from prenatal alcohol are also determined by differences in the vulnerability of the fetus and the quantities and various drinking patterns that it is exposed to. For example, it was reported as early as 1993 that dizygotic twins were differently affected by the same amount of alcohol, but monozygotic twins were not (10). All these factors mean that it is difficult to calculate the risks for individual fetuses.
Light-to-moderate drinking

Despite the fact that there are common agreements on the teratogenical effects of alcohol, there are ongoing discussions about whether there is a safe level that pregnant women can drink (11). After five Danish studies were published in 2012, the media came to the conclusion that light-to-moderate drinking during pregnancy did not harm the fetus, which may makes public health warnings about being careful confusing for women (12). Contrary to the media reports, the authors of the original Danish studies were actually cautious and advised women not to drink alcohol during pregnancy (13). A later meta-analysis found even if a woman didn’t drink daily, her alcohol consumption could still be detrimentally associated with her child’s behaviour problems (14). Studies by Alvik et al showed, in particular, that a pattern of binge drinking very early during pregnancy, before most women knew they were pregnant, had an impact on child behaviour (15). The meta-analysis concluded that there was no known safe amount of alcohol to consume when a woman was pregnant.

Experimental research

Repeated experimental research models have provided indisputable evidence that prenatal alcohol is teratogenic for the fetus, even in small amounts (16,17). These models had the advantage that they were able to control different conditions and exclude other effect-modifying exposure. Despite these findings, there are still natural gaps between experimental research and how they actually apply to humans. A particularly interesting study from Australia, published in 2017, used three-dimensional photographs of one-year-old infants who had been exposed to different amounts of alcohol in the womb and carried out an objective analysis of their faces. This study showed, for the first time, that even low levels of alcohol exposure during pregnancy had a negative effect on
craniofacial development, leading to mid facial recession. This occurred even when the
others stopped drinking after the first trimester (18). These results provided
significant confirmation of previous animal models that showed that being exposed to
alcohol during embryogenesis caused apoptosis in the cranial neural crest cells, which are
mainly involved in establishing facial bones and neurons. This vulnerable time for the
developing fetus starts very early in humans, at 17 to 18 days after conception, and put
the fetus at an unpredictable risk if the woman drinks alcohol before she realises she is
pregnant. These experimental studies showed that different appearances of midfacial
hypoplasia were determined by the fetus being exposed to alcohol at different times
during the pregnancy. In the light of these findings, it would not be advisable to speak
about safe levels of alcohol when so many unpredictable factors are involved.

**Epigenetic effects**

Another aspect of the effects of prenatal alcohol that needs to be considered is its role in
the epigenetic mechanisms of the developing fetus. We have know since the late 1990s
that the environmental conditions in the womb can have an impact on an individual’s
health later in life (19). Epigenetics refers to modifications of deoxyribonucleic acid
(DNA), by methylation, which may alter the modulation of gene expression and cellular
functions. Many studies in rodents have demonstrated that PAE leads to persistent
alterations to ribonucleic acid in the cell and causes changes to gene expression, which
influences phenotypic outcomes. An example of this is the mouse model, where the DNA
methylation-sensitive element within the agouti viable yellow locus regulates coat
colour. Exposing pregnant mice to alcohol during the early gastrulation period altered
the coat color in their offspring, indicating that specific loci are responsive to the effects
of alcohol during development (20). There is emerging evidence from animal models

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that the epigenome is susceptible to the effects of alcohol during its very early development. This affects more than just the brain and can result in developmental programming for some adult diseases. The concept of the developmental origin of health and disease has been put forward to expand the hypothesis of the fetal origins of adult diseases. This concept states that exposing the fetus to a suboptimal environment may lead to an individual being increasingly susceptible to developing diseases in adulthood (21,22). Experimental studies have identified a critical window, where the fetus is susceptible to alcohol intake in the period prior to implantation, which may contribute to chronic disease outcomes. Animal models involving sheep and mice have been subjected to three different models of alcohol exposure: single occasion binge drinking, ad-hoc low to moderate chronic intake throughout pregnancy and periconceptional exposure before implantation. These experiments showed that all three models had an impact on the development of adult diseases, namely: cardiovascular diseases such as hypertension and poorer cardiac recovery after ischaemia; metabolic diseases, including high fasting glucose and insulin, insulin resistance and obesity worsened by a second hit mechanism due to a high fat diet, and renal malfunction, defined as inability to concentrate urine (23-25).

Another study also showed that the brain was affected early by epigenetic reprogramming of the embryo after exposure to alcohol during neurulation, the developmental stage that occurs early in the fourth week after fertilisation. The study showed altered expression of 23 genes in the mouse hippocampus and the asymmetrical brain structure in this area (26). These findings have the potential to be used as biomarkers for FASD in the future.

The results of this basic research are very promising as they will help clinicians to understand what affect alcohol has on fetus during pregnancy. Paediatricians can play
important roles in the field of FASD, as the consequences of PAE have long lasting effects.

However, it is crucial that when clinicians communicate the message that the best advice is no alcohol intake during pregnancy, as the latest research shows is advisable, that they do so in a way that projects empathy without blame. The current uncertainty over the effects of very low concentrations of alcohol on the developing fetus should be a source of reassurance for those women who have consumed a few drinks during pregnancy. However, they should then be advised to refrain from further consumption. It is important that any communications emphasise why this risk reduction is needed.

Changing habits takes time. For example 30 years ago 30% of pregnant women in Sweden smoked, while today that figure is barely 5% (27). Many synergetic factors contributed to this dramatic improvement, but paediatricians, epidemiologists and scientists probably played an important role. Paediatricians need to be more observant when they are dealing with children with FASD and they need to improve their knowledge about how to detect complications in both mental and physical health conditions and rehabilitate those individuals.
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**CONFLICT OF INTERESTS**

The author have no conflict of interests to declare.

**Figure Legends**

Figure 1. A boy with FAS at 2.5 years of age

Figure 2. The same boy at 6.5 years of age