

## Genetic and Epigenetic Perspectives on the Role of Fathers in Fetal Alcohol Spectrum Disorder

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### KEY MESSAGES

Given that fathers who consume alcohol at risky levels may contribute to FASD due to sperm abnormalities and genetic and epigenetic influences, it is recommended that fathers as well as mothers be involved in pregnancy planning and in reducing/stopping at-risk alcohol consumption in the preconception period. Preconception interventions with male partners should be synchronized with those designed to support women in preventing FASD.

### Issue:

Fetal Alcohol Spectrum Disorder (FASD) is a diagnostic term used to describe the impacts on the brain and body of individuals prenatally exposed to alcohol. FASD is a lifelong disability. Individuals with FASD will experience some degree of challenges in their daily living, and need support with motor skills, physical health, learning, memory, attention, communication, emotional regulation, and social skills to reach their full potential. Each individual with FASD is unique and has areas of both strengths and challenges.

The direct exposure of a fetus to alcohol during the prenatal period is an essential requirement for the current Canadian FASD diagnostic guidelines [1, 2]. However, not every mother who drinks during pregnancy will give birth to a child with FASD, suggesting that factors other than maternal alcohol consumption may make the fetus more vulnerable to prenatal alcohol exposure (PAE) and therefore may contribute to FASD.

The potential role of fathers in FASD has had less attention [3-5]. Some researchers have conducted animal studies to investigate the potential role of paternal alcohol consumption in birth outcomes [6, 7]. These studies provide some evidence that fathers' alcohol consumption may indirectly contribute to FASD, as somewhat similar phenotypes to FASD have been found in offspring where exposure has been solely from fathers' preconception alcohol use. Recent advances in genetic and epigenetic research have shed new light on the potential paternal contribution to FASD [8, 9].

**The purpose of this issue paper is to summarize the current research on the genetic and epigenetic perspectives of the potential contribution of fathers to FASD.**

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## Background:

Laboratory research studies show a number of unusual birth outcomes and abnormalities in the offspring of male rats exposed to alcohol without PAE including 'runts' (i.e., small stature), reduced birth weight, organ failure, impaired learning and memory, impaired cognitive functioning, and higher postnatal mortality [10-16]. Therefore, even in the absence of maternal PAE, fathers' preconception alcohol consumption appears to have an impact on birth outcomes, as well as possible cognitive and behavioural impairments in their offspring. Consequences of preconception paternal alcohol consumption in the absence of maternal PAE have also been observed in humans, including increased likelihood of having a smaller than normal head size (i.e., microcephaly) [17] and abnormalities in reproductive hormones and the development of the reproductive system in boys [18].

Researchers have also begun investigating the transgenerational (i.e., parent-child-grandchild) effect of fathers' alcohol consumption. These studies demonstrate that the impact of the fathers' alcohol consumption may be passed on to multiple generations by changes to the male sperm [6, 19, 20]. Based on these observations, preconception alcohol consumption by fathers may result in:

- Changes to the male sperm (e.g., number, shape, and ability to penetrate the egg);
- Changes to the genetic contribution (e.g., changes to the sperm DNA that may be inherited by the children); and
- Epigenetic changes (i.e., alternations beyond DNA) to the gene regions that are inherited from fathers by their children

These implications may change how different genes are switched 'on' and 'off' (i.e., gene expression) in male sperm. Therefore, the contribution of fathers to FASD could be explained by the concept of '*paternal exposome*' [21], which describes the process in which a father passes on the toxic messages he acquired from the environment to his children, in this case, passing on the toxic impact of alcohol exposure.

### 1. Impacts on the sperm

Some researchers have demonstrated alterations to the fathers' reproductive system upon alcohol consumption. Examples include reduced fertility, spermatogenesis (i.e., sperm development), lower sperm count, and irregular sperm shape [11, 22, 23]. These abnormalities in the sperm quality may contribute to negative birth outcomes for fetal and child health, including spontaneous abortion, impaired reproductive development in offspring, low birth weight, and cognitive impairments [4, 24, 25].

### 2. The genetic contribution from the father

The genetic material from the sperm and the egg together determine the genetic makeup of the children. Therefore, genetics are also known to play a role in FASD, more specifically the genes or gene alleles (i.e., variant forms of the same gene) that make a fetus more vulnerable or susceptible to maternal PAE. Genes that have been identified in relation to FASD so far include *ALDH2*, *ADH1B*, *ADH1C*, *HTR2A*, and *CYP2E1* [8, 9, 12, 26]. Additionally, genes inherited from the father that contribute to the thyroid hormone production in the fetus have also been shown to make the fetus more vulnerable to maternal PAE [27].

On the other hand, gene variant forms, such as *ADH1B\*2* and *ADH1B\*3*, have been suggested to contribute to the 'resiliency' of the fetus to maternal PAE. These genes carry the genetic messages required to generate alcohol metabolizing enzymes and thus remove alcohol faster, reducing the potential harm of the alcohol [8, 9].

A balance between genes that make a fetus susceptible or resilient to maternal PAE may determine the likelihood of FASD. Moreover, animal studies using rats have demonstrated that preconception alcohol consumption by male rats can result in fragmentation of their sperm DNA and reduction in the size of the sperm genome compared to male rats who did not consume alcohol [16]. Such changes to DNA size may be an indication of chromosomal abnormalities and mutations that could be transmitted to the next generation.

### 3. Epigenetic changes beyond the DNA level

Epigenetic changes are modifications that happen on the DNA and to the proteins that are bound to DNA, which are referred to as DNA methylation and histone modifications, respectively [28]. Without changing the DNA sequence, these modifications determine whether a gene is switched 'on' or 'off' and thereby may contribute to some of the symptoms of FASD [8, 9, 28].

For example, the *Dopamine Transporter (DAT)* gene is an important gene in the brain that is involved in the transmission of signals between neurons. In one study, DNA methylation of the *DAT* gene was decreased in both fathers with heavy drinking habits and their babies, suggesting that the epigenetic changes caused by preconception paternal alcohol consumption can be passed on to their children [29].

DNA regions known as '*Imprinting Control Regions*' regulate imprinted genes which are switched on or off in children based on the parental origin of inheritance. *H19* and *Rasgrf1* are two examples of such control regions. DNA methylation changes at *H19* and *Rasgrf1* have been reported in the offspring of male rats who consumed alcohol before mating in association with reduced postnatal growth, which was more pronounced in the male offspring of male rats exposed to alcohol [30].

Research studies involving human fathers who are heavy alcohol users also support the hypothesis that DNA methylation changes at imprinted regions caused by paternal preconception alcohol consumption are inherited by their children, and result in some of the visible symptoms similar to FASD [31].

### Implications and Recommendations:

This paper summarizes current research on alcohol and genetic and epigenetic issues related to the potential contribution of fathers to FASD.

- Paternal alcohol consumption prior to pregnancy could result in abnormalities in the fathers' reproductive system, including infertility, reduced sperm quality, quantity, ability to move, and altered shape. These abnormalities may have a negative impact on birth outcomes, fetal development, and child health.
- Fathers' genes that determine genetic susceptibility or resiliency to the harmful effects of alcohol may contribute to the likelihood of the development of FASD.

- Alcohol consumption by the father prior to conception may cause epigenetic changes to genes that are important for fetal development and can be inherited by the children from their fathers.

Note that this paper does not discuss the relational support or hindrance that fathers may offer to their partners that would support FASD prevention. For additional information, please refer to our companion issue paper on the role of fathers in FASD prevention.

## Conclusion:

Therefore, there is evidence that the exposure of fathers' sperm to alcohol can pass on alcohol toxicity and cause phenotypes similar to FASD, and fathers' genetic contribution can play a role in whether the fetus is vulnerable or resilient to maternal PAE. Additionally, epigenetic changes caused by preconception paternal alcohol consumption can be inherited by their children. Thus, we can say that *fathers play a role in making the fetus more vulnerable to PAE and contributing to FASD*. Further research is needed, but based on the available evidence, it is recommended that both parents who plan to be pregnant avoid at-risk alcohol consumption in the preconception period to prevent the possibility of FASD.

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