Alcohol, pregnancy and infant health – a shared responsibility

ALCOHOL AND SOCIETY 2020



A REVIEW OF INTERNATIONAL AND SWEDISH RESEARCH

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Views expressed in this report are those of the authors and do not necessarily reflect those of the organisations that initiate the work.

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Foreword

Of all the lifestyle choices we make in conjunction with pregnancy, none are of greater importance to the child's future health and development than the ones we make in relation to alcohol.

Until now, responsibility for the unborn child's health and well-being has, by and large, lain exclusively with the woman, with recommendations that she abstain from alcohol, smoking, and some types of food. Little has been said about the role of the man or the consequences for the unborn child of his alcohol consumption.

This report aims to emphasise parenthood and the relationship with alcohol as a shared responsibility and an important equality issue. It is important that everyone involved is fully familiar with the potential risks associated with alcohol to ensure they can take informed decisions.

The report has been written by some of the world's leading alcohol researchers, led by Harold Holder. The researchers review international studies and evaluate the scientific strength of the various studies' findings. The research clearly shows that alcohol can cause more foetal damage than virtually any other substance. In every other context, we avoid things that can be hazardous to the unborn child, even in the absence of 100% proof of the potential for harm. This is even more important when it comes to alcohol, where the research findings are clear and the risks substantial.

New research, which is highlighted in the report, shows that a man's alcohol consumption prior to the pregnancy can damage the foetus and impact the child's birth weight and health by causing changes to the sperm's genome.

Foetal damage is one of the clearest examples of the second-hand harm caused by alcohol. The cost of FAS (foetal alcohol syndrome) in Sweden is estimated at SEK 14 billion per annum, calculated on the basis that 0.2% of all children in Sweden are born with FAS. The biggest share of these costs derives from support provided by society.

A great many researchers, paediatricians, midwives, and nurses in Sweden call for increased knowledge and awareness of the risks associated with alcohol. Our aim, through this report, is to help ensure that prospective parents are able to reduce the risks by being better informed. That information is currently lacking and no authority has currently taken responsibility for remedying this deficit.

The most common reaction amongst people who have suffered various types of harm is to wish that they had known more about the risks – that someone had told them. This is a shared responsibility of society as a whole, and the report also stresses the importance of preventative measures at societal level.

And finally, high quality, non-stigmatising interaction is very important. Information should be provided in a respectful way and be adapted to the target group's needs and situation. A lack of information has the biggest impact on the people who need it most.



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Executive summary

Consequences of alcohol exposure in connection to pregnancy

- Alcohol exposure in pregnancy is the most common cause of preventable cognitive deficits among children in Sweden and globally, affecting an estimated 1% to 5% of live births each year
- The most well-known consequence of parental alcohol exposure is foetal alcohol syndrome (FAS), which includes cognitive deficits, abnormal facial features and deficiencies of the central nervous system and growth
- The incidence of FAS in Sweden has been estimated at 0.1% to 0.3% of all births, or 100-300 cases per year, and for FASD 1% to 3%. The cost of FAS to Swedish society is conservatively estimated at €1.4 billion per year.
- Heavy alcohol use during pregnancy is an established risk factor for multiple adverse outcomes including, spontaneous abortion, stillbirth, premature birth, intrauterine growth retardation, low birth weight and sudden infant death syndrome (SIDS). Even low-to-moderate alcohol exposure during pregnancy increases the risk for some adverse outcomes.
- Even though the brain is the organ most severely impacted by prenatal alcohol exposure, abnormalities within the heart, kidney, liver, gastrointestinal tract, and the endocrine system can also occur.
- The effects of prenatal alcohol exposure on foetal development are stronger than those from tobacco use, use of other psychoactive substances and exposure to other hazards such as lead and radiation.
- Possible causal mechanisms include alcohol-induced brain cell death and damage to the DNA of immature male and female reproductive cells, causing changes which can potentially last for generations.

Postpartum effects

- Alcohol does not increase human milk supply and is associated with early cessation of breastfeeding. Alcohol appears to be a risk factor for SIDS, specifically when parents sleep with the baby.
- Firm evidence on the effects of low alcohol consumption while breast feeding is lacking. But even low levels of ethanol exposure can disrupt infant sleep patterns and reduce maternal milk production. Applying the precautionary principle here would suggest it safest to avoid alcohol exposure while breastfeeding. However, consumption of 1 standard drink consumed 2 hours prior to breastfeeding is unlikely to result in significant blood alcohol concentrations in a nursing mother.

Alcohol use in the time surrounding pregnancy

- The natural inclination is to perceive alcohol and pregnancy as a problem restricted to pregnancy, and a problem restricted to women. Neither is true. The effects of alcohol on pregnant women and their offspring are related to the alcohol use of both men and non-pregnant women in the general population.
- Over 80% of Swedish women drink alcohol during the year prior to pregnancy and 14% drink at heavy levels. Overall, few women reduce consumption prior to pregnancy recognition.
- Male drinking in the pre-conception period may adversely affect the foetus and possibly subsequent generations through genetic modification of sperm.

Evidence for effective policies

- Policies that restrict the availability, affordability and marketing of alcohol have been shown to effectively reduce heavy drinking (e.g., binge drinking) and alcohol-related harms in the general population. This includes drinking among those of reproductive age and effects on pregnancy and infant health have been demonstrated.
- Evidence of the potential risks of adverse outcomes associated with drinking during pregnancy should be widely promoted to the general population to support informed decision-making by policymakers and consumers. Women who choose to drink during pregnancy should not be stigmatized or reported to authorities by health care providers.
- Guidelines in many high-income countries advocate abstinence from alcohol as the safest course throughout pregnancy.
- There is mixed evidence for effects of low-dose alcohol consumption in pregnancy (i.e., 'moderate' drinking) from a variety of human and animal studies. On balance, however, the evidence for effects of low-dose alcohol consumption in pregnancy suggests that abstinence is the safest choice.



Alcohol exposure in pregnancy is the most common cause of preventable cognitive deficits among children in Sweden and globally.

Key recommendations

- Policies which reduce the availability, affordability and marketing of alcohol are needed to sustain a low risk environment for alcohol-related birth abnormalities.
- There is a shared responsibility for society at large and healthcare providers to raise awareness of the risks of prenatal alcohol exposure and provide support to pregnant women and their partners to manage these risks and their consequences.
- Persons planning a pregnancy, women as well as their partners, can improve the probability of a healthy pregnancy outcome by abstaining or minimise alcohol exposure.
- It is safest to abstain from any alcohol consumption during pregnancy. Partners may also choose to abstain from drinking during this period, and if they choose to continue drinking they should do so within low-risk guidelines.
- It is also safest to avoid alcohol exposure while breastfeeding. Those who choose to drink during breastfeeding should limit consumption to 1 standard drink, consumed 2 hours prior to breastfeeding.
- An expert national centre should be established in Sweden charged with developing strategies to reduce prenatal alcohol exposure, monitor prevalence of exposure and provide training in screening and treatment.

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1 Alcohol, pregnancy and infant health: a shared responsibility

1.1 Overview and background

Worldwide and in Sweden, alcohol-exposed pregnancies remain a key preventable public health problem that leads to a variety of medical, social and economic harms. The causes and determinants of alcohol-exposed pregnancies are both generated and borne by society as a whole; they involve men and women, and the root of the problem lies in population-level drinking patterns outside of pregnancy, which are highly correlated with those during pregnancy across populations. Accordingly, current approaches to the prevention of alcohol-exposed pregnancies suffer by neglecting the important contributions of alcohol consumption and excessive drinking among those of reproductive age who are not yet pregnant or not aware they are pregnant, and by neglecting the role that men play in alcohol-exposed pregnancy, foetal health, and child wellbeing and development.

Pregnancy is a special time of life for expecting parents during which a number of lifestyle changes may become necessary. These may include social, psychological and economic adjustments, but also adjustments in some health behaviours including diet, smoking, the use of alcohol and also other psychoactive substances.

In modern life, consumption of alcohol is often important in socialising and may be perceived as a source of enjoyment and relaxation. Changing alcohol habits, especially abstaining from alcohol, can be difficult as this may challenge prevailing social norms. This means it can be challenging to provide credible advice to pregnant parents on how to manage these changes. It also gives reason to challenge these norms and for society at large to consider how to manage consequences of alcohol use and to develop policies that can minimize harm. The value of developing strategies that inform and support people planning a pregnancy, and the importance of cost-effective public health action, e.g. legislation that reduces the overall availability of alcohol should not be overlooked.

1.1.1 *The precautionary principle*

One question to be addressed here is whether restrictions on or abstention from alcohol during pregnancy are necessary and supported by evidence from rigorous research. In this report we review the literature on the effects of parental alcohol exposure before, during and after pregnancy, including effects



The causes and determinants of alcohol-exposed pregnancies are both generated and borne by society as a whole



on the fetus, the mother and the father. We also consider some of the wider literature linking population level consumption as well as policies to reduce alcohol availability or affordability with birth outcomes.

Rapid growth and cell proliferation of the foetus as well as dependence on the nutritional status and environmental exposure of the mother makes the unborn child highly vulnerable to adverse effects of potentially toxic substances, even in small amounts. Common advice given to women undergoing prenatal care is to abstain from a range of foods and exposures that may adversely affect the health of the foetus, even though the risk of harm may be very small. In order to avoid contracting listeriosis for instance, a rare disease which affects about 8.6 in 100,000 live births in USA[1], and 1 – 2 pregnant women per year in Sweden[2], pregnant Swedish women are advised to avoid raw or smoked fish, processed cold meats and soft cheeses which may carry the listeria bacteria and potentially result in miscarriage (The Swedish Nationla Food Administration 2008).[3] Women are additionally advised to avoid certain herbal products and nutritional supplements, to limit caffeine intake from coffee, tea and soft drinks and of course, to completely abstain from tobacco use.

During breastfeeding, women are often advised to avoid eating fish that may contain high levels of mercury, limit caffeine intake and avoid certain medications. Indeed, administration of medications of any type are treated with extra caution during pregnancy and breasfeeding. The US Food and Drug Administration for instance lists specific categories for chemical hazards and prescription drug labelling for pregnancy, the most adverse of which is referred to 'Catergory X', and described as drugs where 'studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefit'.[4] Corresponding system for medications exists also in Sweden.[5,6]

Application of the precautionary principle is therefore well established and widely agreed upon as appropriate where pregnancy and newborns are concerned.

1.1.2 *Foetal and infant health and substance use*

Behaviours during the period before and around conception by both parents can have a striking impact on the future health of the unborn baby with implications that will be experienced across their entire life course. Recent reviews conclude that this period is strongly associated with an increased risk of chronic disease in offspring.[7–9] In many cases, the evidence is quite clear. Heavy alcohol exposure during pregnancy is the most common cause of preventable cognitive impairment globally, estimated to affect 1–5% of live births each year.[10] Foetal alcohol exposure leads to a number of neural and behavioural disorders that have been extensively documented in the human scientific literature and supported by studies using animal models. Adverse pregnancy outcomes include stillbirth, spontaneous abortion, premature birth, intrauterine growth retardation and low birth weight and can result in a range of lifelong conditions known as foetal alcohol spectrum disorders (FASD).

The US Institute of Medicine in 1996 published a compilation of environmental exposures that pose threats to foetal health. These included methyl mercury, ionizing radiation, phenytoin, PCBs, lead, opioids, marijuana and tobacco as well as alcohol. Negative outcomes included gross neuropathology, cognitive deficit, reduced IQ score, hyperactivity, attention deficit, developmental delay, gait abnormality, fine/gross motor coordination, sensory deficits and neonatal withdrawal. In this review alcohol stood out uniquely as the only substance where associations with all these negative outcomes are found. Of all the psychoactive substances considered, including heroin, cocaine, and marijuana, alcohol was associated with by far the most serious neurobehavioral effects in the foetus, see table 1.[11]

TABLE 1 Neurobehavioral Outcome of Prenatal Exposure in Humans or Animals

	Alcohol	Methyl-mercury	Ionizing Radiation	Phenytoin	PCBs	Lead	Opioids	Marijuana	Tobacco
Gross neuro-pathology	+	+	+	–	–	0	0	0	0
Mental retardation	+	+	+	0	?	0	0	0	0
Reduced IQ scores	+	+	+	+	+	+	0	?	+
Hyperactivity	+	–	–	–	+	?	0	0	+
Attention deficit	+	–	–	–	–	?	?	+	+
Developmental delays	+	+	–	+	+	–	?	+	+
Gait abnormality	+	+	–	–	0	0	0	0	0
Fine/gross coordination	+	–	–	–	+	?	?	0	0
Sensory deficits	+	+	–	–	0	+	0	0	+
Neonatal withdrawal	+	–	–	–	–	–	+	?	+

+ = Positive findings **?** = suspected, some reports **0** = no effects **–** = not tested, unknown

From: Kathleen Stratton, Cynthia Howe, and Frederick C. Battaglia, Editors. *Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment.* Committee to Study Foetal Alcohol Syndrome, Institute of Medicine, National Academy of Science, Washington D.C. 1996.



Recent estimates are that worldwide, around 119,000 children are born with FAS each year.

1.1.3 *Prevalance and social costs of alcohol-caused congenital conditions*

Recent estimates are that worldwide, around 119 000 children are born with FAS each year.[12] The highest rates of FAS can be found in Europe at 37.4 per 10,000, compared with a global estimate of 15 per 10,000 births. However, the prevalence of FASD – which covers hundreds of alcohol-caused congenital conditions spanning many body systems including brain, heart, kidneys, liver, digestive tract and endocrine system – is about 10 times greater than FAS[13], indicating that the global prevalence of FASD maybe around 1.5% and almost 4% in Europe. It is not clear how many people meet the criteria for the various FASD-related conditions in Sweden. The latest Swedish prevalence study was performed in the late 1970s[14] and reported prevalence of FAS between 0.2% and 0.3% which suggests the prevalence of FASD may be in the region of between 2% and 3% of the population. Other estimations for Sweden find rates of 0.1% to 0.2% for FAS[12] and 0.7% for FASD.[15]

International cost estimates find a mean annual cost for children with FASD to be $22,810 and for adults $24,308.[16] Based on a prevalence of 0.2%, the cost of FAS to Swedish society was estimated at €1.4 billion per year. The major cost driver was societal support.[17] The authors acknowledge that the prevalence of FAS in Sweden is probably higher than 0.2% and note that the cost estimates do not include FASD. The true societal cost of alcohol-caused congenital conditions is therefore likely to be considerably higher. A recent Canadian study reported the total cost of FASD to Canadian society as $9.4 billion per year.[18]

1.1.4 *Swedish attitidudes to drinking during pregnancy*

A Swedish study using focus groups, with young, non-pregnant, non-parous women to explore their attitudes towards alcohol consumption during pregnancy, found that while most women supported the concept of complete abstinence from alcohol during pregnancy, they also reported several reasons why this would be difficult.[19] For instance, 'If you choose not to drink, many will suspect that you are pregnant.' Much ambivalence was expressed concerning the timing of exposure. On the one hand, many women thought that the responsibility for the child starts with pregnancy planning; if pregnancy is the aim then alcohol should be avoided. On the other hand, it was reasoned that it could be difficult not to drink as conceiving could be a long process. When not actively trying to conceive, women did not see a need to adjust their alcohol use. Women were unsure about specific outcomes related to alcohol exposure during pregnancy and only a few used the term FAS. In contrast, participants in an American focus group study with pregnant and non-pregnant women could describe the problems caused by alcohol exposure during pregnancy in all 20 of the groups included in the study. This is likely due to stronger efforts to highlight the problems of FAS in the US compared with Sweden.

In addition, another study found that during their partner's pregnancy most men did not adjust their lifestyle to improve health and fertility, while some made several changes. Both pregnancy-planning behaviour and fertility knowledge seem to be related to level of education and mode of conception.[20]

1.2 Research methods and limitations

Attributing poor birth outcomes to prenatal alcohol exposure is a complicated and ongoing task. It is important to understand the limitations inherent in this type of research.

It has been widely reported that when surveyed, individuals typically underreport their own alcohol consumption due to a range of factors including recall bias, social desirability and perceived norms. This may be particularly true during pregnancy when drinking may be associated with shame. Drinking behavour is also linked to many psychosocial

background factors that can confound results from studies of alcohol use and pregnancy, including socioeconomic status; levels of stress; and comorbid mental health conditions. All of these associated factors have been shown to increase the risk of poor pregnancy outcomes, including spontaneous abortion, stillbirth, preterm delivery, and, in some cases, SIDS. However, the association between alcohol exposure during pregnancy and birth outcomes has been confirmed in animal studies without the limitations that apply to human research, giving stronger credence to a causal association between prenatal alcohol exposure and poor pregnancy outcomes.[21]

Randomised controlled trials are generally considered the gold standard when attempting to estimate causal effects of exposure to a substance. However, for many public health issues, including prenatal alcohol exposure (PAE), randomisation of exposure is unethical and/or unfeasible and, therefore, it is necessary to rely on observational data. To increase the reliability of observations, triangulation of different methods can be performed, where, for instance, "Mendelian randomization" studies can be included. These types of studies examine differences in risk for diseases as a function only of genetic variation which serves as a proxy for alcohol exposure, and of course, should not be influenced by environmental and sociodemographic factors. The advantage of triangulation is that biases are assumed to differ across the diverse study types. Confidence in causal inferences is increased where similar effect estimates are obtained across different study types.[22]

1.3 National competence centre

In Sweden there is no specific national competence center for FASD. The Swedish Family Care Competence Centre, SFCCC, (Nationellt kompetenscentrum anhöriga) have nevertheless published a review on FAS.[23] There is also a FAS society that with support from National Board of Health and Welfare have set up a FAS information website[24] together with Swedish physicians and researchers. But there is no ongoing epidemiological surveillance to shed light on levels of alcohol exposure before, during and following pregnancy, nor of the prevalence of FAS and FASD, and the resulting clinical complications from these conditions. In addition to this monitoring function, a national center could also be a resource center, to which individual children could be referred for assessments and treatment, and also a training center where training could be offered for clinicians, social workers and teachers on strategies for identification, diagnosis and treatment of these conditions.[25]

1.4 Ethical Issues for Prevention Strategies

One important issue concerning strategies directed at prevention of FASD is the potential to stigmatize pregnant women both before and after giving birth. It is certainly possible that some pregnant women may avoid prenatal care for fear of being disrespected or reported to social services. In this way, prevention efforts and reporting requirements can have the exact opposite effect to that which was intended, that is, to reduce the risk of harm from alcohol exposure during pregnancy.[26]

After release of a study finding no adverse effects of low volume alcohol exposure during pregnancy on behavioural outcomes for their children, a British healthcare ethicist argued that the total abstinence policy during pregnancy sat uneasily with these study findings and was ethically problematic. He further argued, that the "precautionary" approach advocated by many health advisory bodies displayed both scant regard for the autonomy of pregnant and prospectively pregnant women and a confused grasp of the principle of doing no harm.[27]

It is not the intention of this report that parents should be stigmatized or reported to authorities by health care providers. Rather, evidence of the potential risks of birth complications associated with alcohol exposure during pregnancy should be fairly presented

to everyone with the recognition that, in the end, this is an informed decision to be made by individuals. This also applies to communicating the level of certainty around risks, acknowledging uncertainty (e.g. in relation to low volume drinking) and respecting the autonomy of women to make informed decisions about their health.

There are indeed some uncertainties in the evidence base in relation to the effects of low-to-moderate level alcohol exposure. We suggest these are not overlooked but acknowledged in public discourse. However, laboratory evidence of the potential for even small amounts of alcohol to damage the foetus is in our view sufficient to warrant application of the precautionary principle and recommend that pregnant women completely avoid alcohol. It would not be acceptable in relation to any other risk factors (e.g. lead or arsenic) for governments to take no action or for potential risks not to be communicated.

We have also adopted the perspective that the issue of reducing alcohol exposure before and during pregnancy is a responsibility that is shared with partners and the community at large. It becomes a shared responsibility, therefore, of partners, family members, friends as well as establishments serving alcohol and, critically, of public health authorities to ensure the reality of the risk is communicated in a clear but supportive and non-stigmatising manner.



2 Alcohol Consumption Apart from Pregnancy or Prior to Pregnancy Recognition

The natural inclination is to think of alcohol and pregnancy as a problem restricted to pregnancy, and a problem restricted to women. Neither is true. The effects of alcohol on pregnant women and their offspring neither begin nor end with pregnancy itself, and are related to alcohol consumption of both men and non-pregnant women in the general population, and of women prior to pregnancy recognition. This section therefore focuses on the importance of alcohol consumption among those of reproductive age who are not known to be pregnant.

2.1 Alcohol Consumption Outside of Pregnancy, Including the Preconception Period

Women do not suddenly start drinking alcohol, or drinking heavily, when they become pregnant. Appreciating this fact is absolutely critical to the prevention of alcohol-exposed pregnancies and alcohol-related impacts on mothers and their children. Rather, those who drink during pregnancy were drinkers prior to becoming pregnant. So prior drinking, and prior heavy drinking in particular, are strong risk factors for drinking and binge drinking during pregnancy.[22,28] A review of 14 studies originating from the US, Europe, Australia, New Zealand, Japan and Uganda found that pre-pregnancy drinking is one of the strongest predictors of drinking in pregnancy.[29] More recent studies[30–32] from Australia and New Zealand show similar correlations, adding that pre-pregnancy drinking also predicts alcohol consumption straight after birth at a time when safe breastfeeding should be encouraged.[30] Some proportion of those who drink during pregnancy (approximately one-quarter to one-third) will binge drink or drink heavily during pregnancy.[33,34] Viewed the other way around, the prevalence of drinking and binge drinking in pregnancy is a direct function of the prevalence of drinking and binge drinking in the general population among persons of similar age. In Sweden in 2018, the prevalence of hazardous drinking was 20% and 11% among women from 17–29, and 20–44 years, respectively.[35]

2.1.1 *Paternal contributions to health and wellbing of mothers and infants*

Paternal drinking also has a profound impact on the health and wellbeing of expecting mothers, foetuses and their living children. Women are more likely to continue to drink during pregnancy if they have a live-in male

20%

In Sweden in 2018, the prevalence of hazardous drinking was 20% and 11% among women from 17–29, and 20–44 years, respectively



There is evidence to suggest that women of male partners who are more supportive and actively involved in the pregnancy are more likely to follow health advice including reducing alcohol use.

partner who drinks and this is particularly so if the male partner is a heavy or risky drinker. Moreover, relationship dissatisfaction or disfunction can also influence whether a woman continues to drink during pregnancy.[36] There is evidence to suggest that women of male partners who are more supportive and actively involved in the pregnancy are more likely to follow health advice including reducing alcohol use.

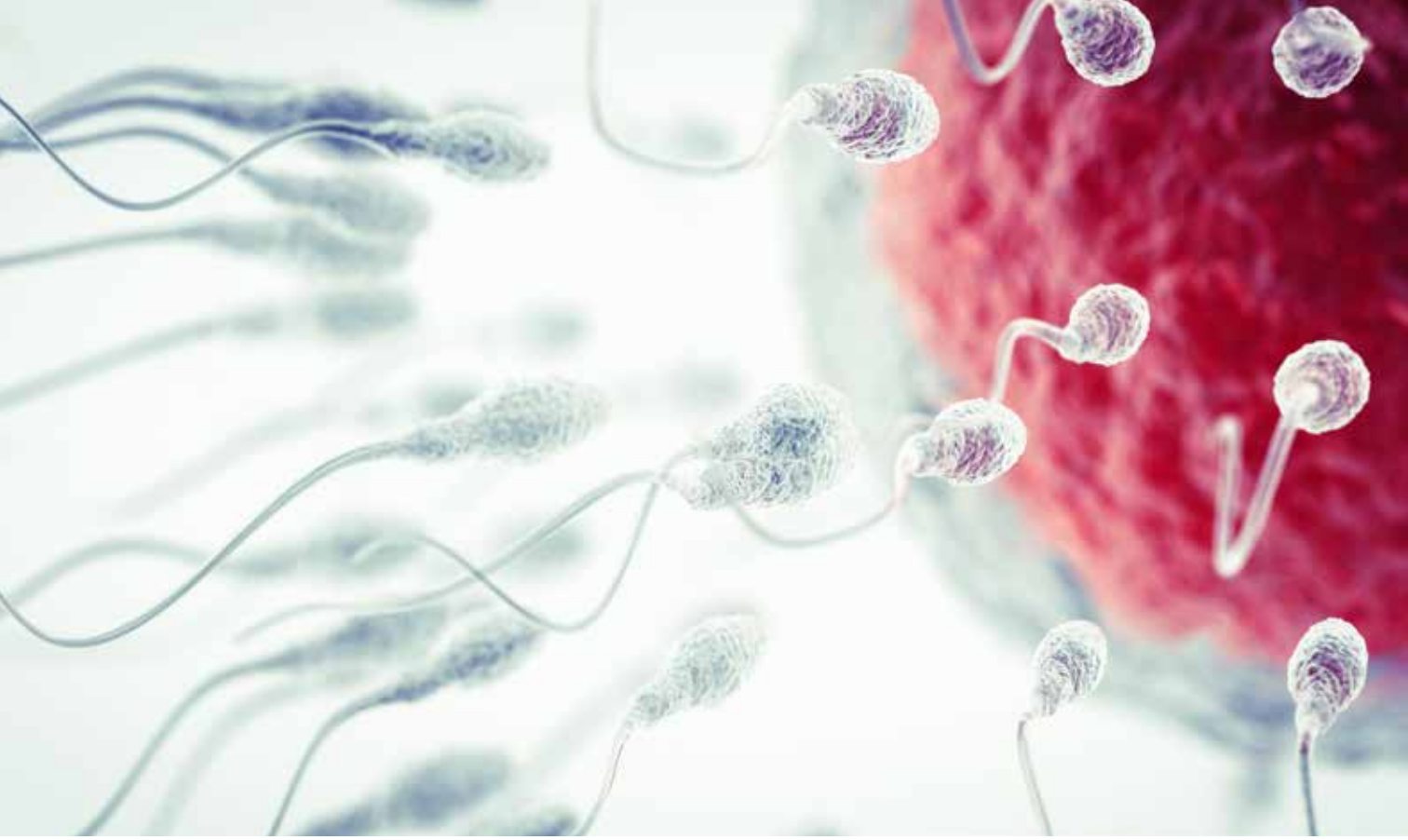
Acute alcohol intoxication among men is associated with the perpetration of sexual assault (and therefore rape-related pregnancy), unplanned consensual sexual encounters, and a lower likelihood of using condoms.[37–40] All of these may increase the risk of unintended pregnancy and the possibility of an alcohol-exposed pregnancy prior to pregnancy recognition. For example, a Swedish study found that binge drinking among men is associated with intimate partner violence and a nine-fold increase in the risk of intimate partner violence during pregnancy.[41] In Sweden in 2018, the prevalence of hazardous drinking was 25% and 17% among males from 17 – 29, and 20 – 44 years of age, respectively.[35]

Emerging scientific evidence also points to the importance of paternal drinking on sperm volume and uncertain effects on sperm density, count, motility, and morphology.[42–44] A US IVF-based study showed that even at very low doses (one can of beer), paternal alcohol consumption in the week before sperm collection resulted in higher risk of spontaneous abortion and still birth.[36] Other studies have found increased risk of: acute lympho-blastic leukemia from paternal but not maternal alcohol intake in the 12 months prior to conception[45]; increased risk of congenital heart disease from maternal and paternal alcohol exposure with a larger risk increase with paternal alcohol intake[46]; ventricle malformation with daily preconception paternal alcohol consumption[47]; and abnormal situs with paternal pre-conception alcohol use.[47] Through a variety of possible mechanisms, children of heavy drinking men also have worse educational outcomes, and increased alcohol-related mortality risk.[48]

2.2 Alcohol Consumption Prior to Pregnancy Recognition

Drinking patterns among women of childbearing age also matter in terms of generally unintended foetal exposure to alcohol during the period prior to pregnancy recognition or confirmation – i.e., the time during which a woman is pregnant but is not yet aware. This is an important issue that potentially applies to all drinkers, including the majority of women who plan to discontinue drinking once they become aware of their pregnancy. There are limited international data, but in the U.S. for example, the median time to pregnancy recognition is about 5 weeks. Women who binge drink during the past 30 days do so 3 – 4 times on average. Among binge drinkers, this might result in an average of about 4 episodes of high-blood alcohol concentration exposures for the foetus. Binge drinking may also be associated with increased time to pregnancy recognition (and hence greater inadvertent ethanol exposure to the foetus) either directly or through the association of binge drinking with higher rates of unintended (i.e., mistimed or unwanted) pregnancies.[22] Unintended pregnancy is itself associated with delayed pregnancy recognition and high rates of therapeutic abortion.[28] It is also possible that the perception of increased neurological risk to the foetus from binge drinking early in pregnancy may be a factor in choosing to have a therapeutic abortion.

In Sweden, a questionnaire study conducted among antenatal care centers found 84% of women reported alcohol use during the year prior to pregnancy; about 14% were categorized as having hazardous consumption, here defined as a weekly consumption > 9 standard drinks containing 12 grams of pure alcohol or drinking more than 4 standard drinks at the same occasion. Of the women who were hazardous drinkers before pregnancy, only 19% reduced their alcohol consumption when



planning their pregnancy compared with 33% of women with moderate alcohol consumption prior to pregnancy. Overall, a low percentage of women reduced consumption prior to pregnancy recognition.[49]

Could one or more high BAC exposures (i.e., binge drinking episodes) have meaningful adverse foetal effects such as neurological problems or foetal loss?[21,50] The periconception and pre-implantation windows, which include maturation of the oocyte, fertilisation, and morphogenesis of the pre-implantation embryo, are particularly sensitive times of development. Within the oviduct and uterus, the embryo is exposed to a unique nutritional environment to facilitate its development and establish de-novo expression of the genome through epigenetic reprogramming. Alcohol has wide-ranging effects on cellular stress, as well as hormonal, and nutrient signalling pathways, which may affect the development and metabolism of the early embryo. Pre-implantation development – the week or so after the oocyte has been fertilized by the sperm and before the embryo implants – represents a vulnerable time as the embryo progresses from the fallopian tube to the uterus. Although limited, studies find that binge-like alcohol doses taken during the initial stages of embryo development triggers the onset of morphological and growth defects observed later in development. These negative effects are marked by DNA methylation alterations in diseases and aging, genome-wide ethanol-induced DNA methylation changes could potentially enhance later risk of health complications.[51]

A Danish study on effects of moderate alcohol exposure and a single episode of binge drinking found that FASD facial phenotypes were 2.5 times more likely among children with a single binge exposure in gestational weeks 3 – 4 compared to children with no such exposures.[52] A review by the U.S. Centers for Disease Control and Prevention of eight studies that included over 10,000 children aged 6 months to 14 years found that any binge drinking during pregnancy was associated with the child having cognition-related problems.[53]

3 Alcohol exposure during pregnancy

40%

A large study of more than 600,000 births found a 40 percent increase in likelihood of stillbirth for women who consumed any amount of alcohol compared with those who did not consume any alcohol.

Heavy alcohol use during pregnancy has been established as a risk factor for multiple adverse pregnancy outcomes, including stillbirth, spontaneous abortion, premature birth, intrauterine growth retardation and low birth weight. Studies find that even low-to-moderate exposure during pregnancy may increase risk for some adverse outcomes.

While studies in humans may be compromised by failing to control adequately for other risk factors associated with poor birth outcomes (e.g. such as older age, lower income in the case of spontaneous abortion), animals studies confirm the association and indicate that observed effects in human studies are very likely to be causal. Since mechanisms of harm have been demonstrated that impact on the functioning of genes regulating the growth and development of the placenta, foetus and stem cells (figure 1)[54], there are implications for both immediate and long term effects on overall growth and also the development of individual organs.

3.1 Access to prenatal medical care

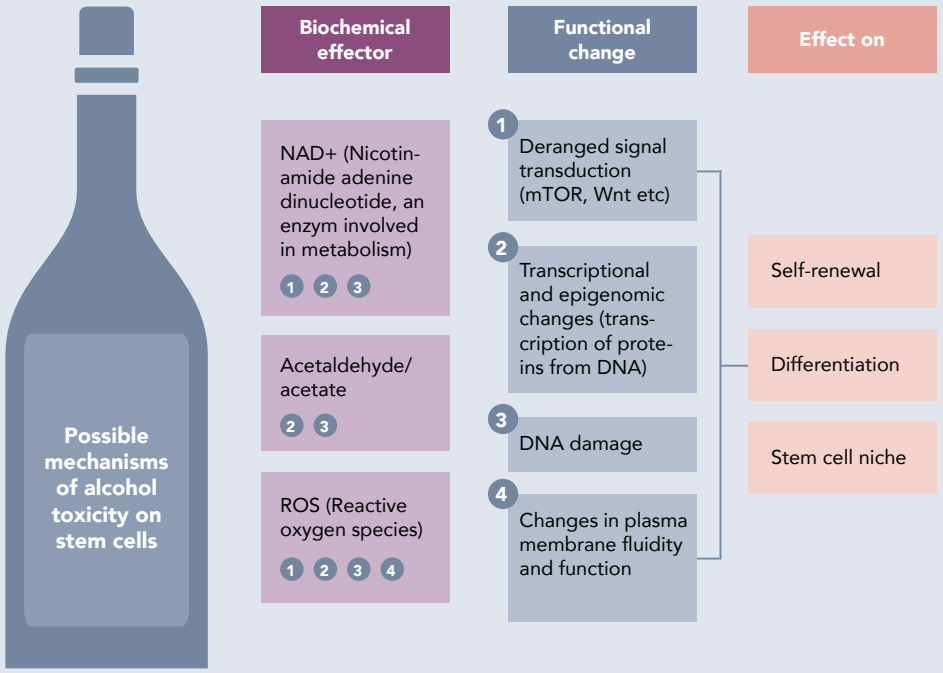
Alcohol exposure during pregnancy may also have consequences for women's access to care during this critical period. There is limited research on this topic, but some researchers have argued there may be unintended negative consequences of policies designed to highlight the risks of alcohol consumption during pregnancy. There is concern in particular that women may feel stigmatised and therefore be less likely to access prenatal care.

3.2 Medical complications during pregnancy

Alcohol use at any level during pregnancy may increase the risk of miscarriage, stillbirth, preterm delivery, and sudden infant death syndrome (SIDS). A large study of more than 600,000 births found a 40 percent increase in likelihood of stillbirth for women who consumed any amount of alcohol compared with those who did not consume any alcohol. This is supported by animal studies which also point to an association between prenatal alcohol exposure and stillbirth.[21] In addition, alcohol use combined with smoking during pregnancy seems to have a synergistic effect on preterm birth, low birth weight and growth restriction.[55]

The strength of the association between alcohol and premature birth remains under debate, because several studies have failed to demonstrate significant effects. However, evidence for a link is strengthened if potential flaws in study design are accounted for, and is particularly strong where alcohol exposure during pregnancy has been at heavy or binge drinking levels.[56] Studies to date do not

FIGURE 1 Possible mechanisms of alcohol toxicity on stem cells



From: Di Rocco G, Baldari S, Pani G, Toietta G (2019) Stem cells under the influence of alcohol: effects of ethanol consumption on stem/ progenitor cells. *Cell Mol Life Sci 76*, 231–44.

demonstrate a link between low-to-moderate drinking during pregnancy and the risk of premature delivery, but multiple studies demonstrate a two- to threefold increase in the risk of premature delivery for women who drink heavily or binge drink during pregnancy. Furthermore, compared to women who do not drink during pregnancy, risk of extremely premature delivery (earlier than 32 weeks) may be as much as 35 times higher heavy drinkers.[57]

There is clear concensus in the scientific literature that heavy alcohol exposure is a cause of low birth weight. However, the evidence for low-to-moderate alcohol use during pregnancy on low birth weight is somewhat inconsistent. While many studies find a clear association others either do not support an association or even find a protective effect at low levels. Nevertheless, the evidence does appear to be more heavily in favour of a negative effect of low-to-moderate alcohol exposure on birth weight with a systematic review of 15 cohort and 4 case-control studies concluding that a significant dose-repsonse relationship exists between alcohol and low birth weight beginning at 10g per day.[58]

In conjunction with two US Committees on Substance Abuse and Fetus and Newborn, Behnke and Smith (2013) conducted a notable review of the effects of various mood-altering substances including nicotine, marijuana, opiates, cocaine, methamphetamine and alcohol on short- and long-term problems in foetal growth, cognition and behaviour. They found that among the scientific literature for psychoactive substances and pregnancy, alcohol is the most widely studied and evidence

of its wide-ranging effects on foetal and child health is strongest.[59] (see Table 2 below).

3.3 Increased risk of domestic violence

Heavy alcohol use by women and their partners is also associated with an increased risk of domestic violence which in turn has implications for the health of women and their babies during pregnancy. Serious long-term effects of violence include impacts on physical, psychological, reproductive and sexual functioning in adults and deprivation or neglect in children. In general, female victims appear to be especially vulnerable to longer-term health consequences of violence.[60]

Research from high-income countries shows that alcohol consumption by either or both victims and perpetrators of violence is associated with greater injury severity[61] and alcohol can be found in approximately 50% of both perpetrators and victims.[62] Alcohol is more closely linked to murder, rape, and assault than any other mood-altering substance, and was a contributing cause in most homicides arising from personal disputes or arguments.[62] Prior to a violent incident alcohol is usually consumed by between one-third and one-half of perpetrators.[63] Women are especially likely to be the victims of murders committed by an intimate partner. Pregnancy has been identified as a time when women are at higher risk of being assaulted by their partners[41], with a world-wide prevalence rate of 28% for emotional abuse, 14% for physical abuse and 8% for sexual abuse.[64] Risk factors for domestic violence during pregnancy include the pregnancy being unwanted, being unmarried and having low socio-economic status.

TABELL 2 Summary of effects on prenatal drug exposure

	Nicotine	Alcohol	Marijuana	Opiates	Cocaine	Metham-phetamine
Short-term effects/birth outcome						
Fetal growth	Effect	Strong effect	No effect	Effect	Effect	Effect
Anomalies	No consensus on effect	Strong effect	No effect	No effect	No effect	No effect
Withdrawal	No effect	No effect	No effect	Strong effect	No effect	*
Neurobehaviour	Effect	Effect	Effect	Effect	Effect	Effect
Long-term effects						
Growth	No consensus on effect	Strong effect	No effect	No effect	No consensus on effect	*
Behaviour	Effect	Strong effect	Effect	Effect	Effect	*
Cognition	Effect	Strong effect	Effect	No consensus on effect	Effect	*
Language	Effect	Effect	No effect	*	Effect	*
Achievemant	Effect	Strong effect	Effect	*	No consensus on effect	*

* Limited or no data available

From: Behnke M, Smith VC (2013) Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics* 131, e1009–24.

3.4 Foetal and infant health

3.4.1 Decreased ability to process alcohol

When alcohol is ingested during pregnancy, it rapidly passes through the placenta to the foetus. Foetal blood alcohol levels rise quickly, attaining equilibrium at around 2 hours after initial exposure[65] and may exceed the mother's blood alcohol concentration. Basically all alcohol in foetal blood is metabolised through the placenta and the mother. Decreased ability to process alcohol in the foetus is attributable to the following:

- The foetus has very low levels of alcohol dehydrogenase activity (ADH), the pathway in adults for metabolising alcohol. Prior to week 16, the foetus has zero capacity to metabolise alcohol.[14,66,67]
- The foetus has an extremely low alcohol elimination rate via the placenta that is only 3 – 4% that of the mother. Un-metabolised alcohol is excreted unchanged into the amniotic fluid and is then reabsorbed into the foetal blood either through swallowing of amniotic fluid (from gestation week 11), or by re-absorption through the skin (up to gestation week 20).[65]

3.4.2 Foetal alcohol spectrum disorder (FASD)

Alcohol exposure during pregnancy is the most common cause of preventable intellectual disability in the world, estimated to affect 1 – 5% of live births each year.[10] The collective expression for foetal consequences of *in utero* alcohol exposure is Foetal Alcohol Spectrum Disorder (FASD). The most specific and well-known consequence of parental alcohol exposure is foetal alcohol syndrome (FAS), which includes not only features of intellectual disability of various degrees, but also typical abnormal facial features, growth problems and problems with the central nervous system (see box). Though less specific, FASD includes the contribution of alcohol to learning disabilities, attention deficit hyperactivity disorder, and conduct disorders.

- Abnormal facial features, such as a smooth ridge between the nose and upper lip (this ridge is called the philtrum)
- Small head size
- Shorter-than-average height
- Low body weight
- Poor coordination
- Hyperactive behavior
- Difficulty with attention
- Poor memory
- Difficulty in school (especially with math)
- Learning disabilities
- Speech and language delays
- Intellectual disability or low IQ
- Poor reasoning and judgment skills
- Sleep and sucking problems as a baby
- Vision or hearing problems
- Problems with the heart, kidneys, or bones

From: Basics about FASDs, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, USA, https://www.cdc.gov/ncbddd/fasd/facts.html [2019-07-17]

Additional terms for describing foetal consequences arising from alcohol's impact on the development of different structures through various mechanisms are:

- Alcohol-Related Neurodevelopmental Disorder (ARND), which includes intellectual disabilities and problems with behaviour and learning.
- Alcohol-Related Birth Defects (ARBD), which includes congenital defects of the heart, kidneys or bones, or hearing impairment.

The collective term FASD is not meant for use as a clinical diagnosis. There have been efforts to review the research and develop guidelines for diagnosing FAS and also for other FASDs, such as ARND, but this is difficult as other disorders such as ADHD and Williams syndrome may show similar symptoms to those associated with prenatal alcohol exposure. Symptoms of FASDs can range from mild to severe, and can affect different people diversely. Even though the brain is the most

severely impacted organ, prenatal alcohol exposure also causes several abnormalities within the heart, kidney, liver, gastrointestinal tract, and the endocrine systems.[68] FASD has a broad range of associated conditions, and should be recognised globally as a large public health problem.[69]

Studies find slightly different national prevalences of FAS and FASD. Given the probable under-reporting of alcohol consumption and diagnostic difficulties, figures are likely to be conservative estimates. Although the prevalence and severity of FASD is related to the amount and duration of alcohol exposure during pregnancy, twin studies have shown that despite virtually identical alcohol exposure, foetuses can experience different FASD outcomes.[69,70]



Studies have established that almost every cognitive domain that has been evaluated is affected by prenatal alcohol exposure.

There are many possible biological pathways by which alcohol can harm the foetus, and the impact may differ depending on gestational stage. There are directly harmful effects during the embryonic and foetal stages of development, as well as toxic effects on the placenta, altered genetic expression and protein synthesis, hormonal alterations, and effects on the vascular development of both the placenta (causing hypoxia and growth retardation) and the foetus. Another specific mechanism includes alcohol-induced death of neural cells caused by exposure to alcohol metabolites, which, depending on the developmental stage, can cause a broad range of problems including central and peripheral nervous system and brain-derived hormonal regulation disruption. Moreover, as a mother's body metabolises alcohol, a substance called acetaldehyde is created. Acetaldehyde has toxic and potentially carcinogenic effects on humans and can cross into the foetus via the placenta. Genetic variation in alcohol metabolism of both mother and foetus may lead to differences in the propensity of individuals to develop alcohol-induced organ damage.[10,59,65]

Evidence that the function of stem cells and their descendants could be affected is emerging. Stem cells are cells that can differentiate into all types of specialised cells, and are integral during foetal development as well as in injury repairs in the adult. Recent studies suggest that alcohol exposure may play a role in impairing stem cell properties, thus affecting organ development and injury response in different tissues.[54]

Another potential causal mechanism for alcohol induced harm to the foetus involves what are known as "epigenetic" changes. As mentioned above, these arise from damage to the DNA in immature sperm and eggs, causing genetic changes in reproductive cells with potential impact for future generations.[71–74]

Intra-uterine alcohol exposure can also impair the functioning of genes responsible for regulating brain stress responses. Studies show that female infants exposed prenatally to alcohol can have higher heart rate and negative mood during stress. For males, exposure to alcohol in utero appears to result in higher levels of cortisol during stress.[10]

Alcohol negatively influences the development of blood vessels in the foetal brain by affecting several genes controlling the expression of proteins regulating the formation of the vascular network in the embryo, affecting the ability to provide crucial oxygen and nutrients for the growth of neural cells.[68] Alcohol exposure disrupts not only vascular development in the foetal brain but also in the placenta, which would be a possible mechanism for affecting not only brain development but intrauterine growth overall.[75]

As mentioned, there is a broad range of neurocognitive problems associated with foetal alcohol exposure. These range from less readily discernible symptoms of hyperactivity, attention deficit and learning disabilities to grave intellectual disability. Neuropsychological studies have established that almost every cognitive domain that has been evaluated is affected by prenatal alcohol exposure[76], including dysfunction in learning, emotion, cognition, motor performance, perception, and behaviour.[68]

Even though not all brain-related FASD problems are detectable as changes in phys-

ical form of infants, there are some studies on structure and function of the prenatally alcohol exposed brain. Before neuroimaging technology existed, physiological evidence regarding the effects of FASD on the developing brain in humans was obtained from autopsies. Through these examinations, researchers found severe damage throughout the brain in infants that had been exposed to high levels of prenatal alcohol. Many of these children fail to develop important brain structures, and have extensive and widespread damage which can be found in all parts of the brain, causing overall small brain volumes.[10,68]

Using magnetic resonance imaging (MRI) technology, overall volume reductions in the cranial, cerebral and cerebellar brain areas in individuals with FASD have been reported.[10] The temporal lobes, which are associated with formation of memories, auditory processing, and language comprehension, are affected, as are the parietal lobes and the subcortical region. Structures such as the basal nuclei, and more specifically the caudate nucleus within the basal nuclei, are smaller which leads to insufficient motor control, learning disabilities, and behavioural inhibition. Excessive grey matter has been observed along with a reduction of white matter, as well as reduced formation of protective sheaths around nerves in the spinal cord.[68]

3.4.3 Cancer

As alcohol and its metabolites are known to cause genetic mutations and are carcinogenic, there are grounds to believe that foetal alcohol exposure could increase the risk for both childhood and adult cancer. Few studies, however, are able to show a strong association with cancers among children, perhaps because the prevalence of childhood cancer is very low. The studies that are large enough, including meta-analyses, find a dose-response association between alcohol consumption during pregnancy and acute myeloid leukaemia (AML) risk.[77–79]

3.4.4 Malformations (e.g., heart, lungs, kidney defects)

Other than the brain and nervous system, other organs can also be affected by alcohol during different stages of foetal development. The most vulnerable period for anatomic abnormalities is early in the first trimester, which includes the time segment preceding pregnancy recognition.[80]



3.4.4.1 Heart

Extensive research has been done on the effect of foetal alcohol exposure on congenital heart defects, although conclusions remain inconsistent. Congenital heart defects are structural anomalies of the heart that are present at birth and can disturb the normal blood flow through the heart or surrounding vessels. It is the most prevalent congenital abnormality, accounting for thirty percent of major congenital anomalies.[81] Overall, evidence shows that both prenatal heavy drinking and binge drinking are associated with a threefold increased risk of congenital heart defects, while moderate drinking is associated with a small increased risk for a group of malformations causing the great arteries leading from the heart to be abnormally connected,

abnormally aligned or abnormally related in space.[46,82,83] These defects typically comprise about 10-12% of all congenital heart defects in total.[84] Paternal alcohol consumption is also associated with increased frequency of congenital heart defects, in particular atrial septal defect and ventricular septal defect.[46]

3.4.4.2 Lung

Alcohol exposure during pregnancy damages multiple types of cells in the developing lung and can potentially increase the risk of respiratory distress in the newborn. When exposed to alcohol in utero, there is decreased expression of the surfactant proteins that reduce the surface tension at the air/liquid interface in the lung which means that the newborn may have problems keeping the small air sacs open. There is also reduced function of the cilia, which are hair-like, moving structures for transporting mucus out of the airways.[85] Findings of increased connective tissue in the alcohol-exposed lung raises the possibility that foetal alcohol exposure may increase the risk of lung scarring lesions as well as impaired immune defence. Prenatal alcohol exposure may be associated with infant mortality and increased odds of developing severe infections, especially in infants with very low birth weight.[86]

3.4.4.3 Kidney

There are a range of anomalies in the urinary system among patients diagnosed with FASD. These include an underdeveloped or even absent kidney[87,88] and impaired kidney function even without any physical abnormalities.[89] Possible mechanisms for impaired kidney function are via effects on the functionality of cells regulating pH, water, and electrolyte balance of the urine that is secreted.[90]

3.4.4.4 Liver

Prenatal alcohol exposure can cause alteration of liver protein synthesis and enzyme activity[91], and has been shown to be a cause of jaundice in newborns.[87] Animal studies suggest there may be an increased risk for non-alcoholic fatty liver disease and altered glucose metabolism[92], but there are no studies in humans confirming this association.

3.4.4.5 Gastrointestinal tract

Alcohol can also cause chronic blockage of the intestine such that they are unable to contract in order to push food, stool, or air through the tract.[93] This can cause abdominal pain and constipation, with the symptoms mimicking a condition known as Hirschsprung's disease, where a section of the colon lacks nerves controlling the muscles and needs to be removed surgically.

3.4.4.6 Immune function

One of the important mechanisms for alcohol's influence on foetal development is increased oxidative stress. Excessive free radicals may cause damage to DNA, cells and proteins, and upset signalling pathways and functions of cells in the immune system. Studies indicate that some immune cells are primed by low-to-moderate foetal alcohol exposure, leading to abnormal immune responses. This may underlie a susceptibility to develop severe infections, autoimmune disease and inflammatory conditions following immune challenge in adulthood.[85,94]

3.5 Effect of Low-Dose a.k.a. "Moderate" Consumption in Pregnancy

There is controversy surrounding the effect of low-dose alcohol consumption in pregnancy (i.e., 'moderate' drinking), with mixed results depending on the study design and the types of outcome assessed.[95–97] There seems to a growing belief that it is fine to drink presumably low amounts of alcohol in pregnancy because of a perception that there is not compelling evidence of harm for neurodevelopmental outcomes.[98–100]

Observational (i.e., non-randomized) studies find that there are small but significant associations between moderate drinking and spontaneous abortion, small for gestational age, possibly preterm birth, and possibly

conduct problems.[53,101,102] For other outcomes related to developmental milestones and educational attainment, results are mixed with overall null associations and even some negative associations among those drinking very low amounts of alcohol compared to those drinking none i.e. implying protective effects of low dose alcohol. There are a number of important caveats to consider.

Because such studies are not randomized, they are susceptible to confounding, in which characteristics of mothers who are drinking low amounts (i.e., having higher education, social status, etc. as is currently the case in developed nations) may contribute to favourable outcomes, rather than any effect of the alcohol itself.

Second, the outcomes that are measured in these epidemiological studies are relatively crude, and reviews comment on the relative lack of studies in this area and also the need for high-quality studies. Therefore, a lack of clear detrimental effect among some outcomes does not preclude more subtle forms of damage or impairment.[53,101,102]

Third, there may be later-in-life outcomes that are not typically assessed in studies of infant and child outcomes, e.g., mental health problems in adulthood.[103]

Fourth, Mendelian randomization studies, which are less subject to bias from confounding than observational studies, find only positive associations with alcohol exposure and adverse outcomes, without beneficial effects even at low doses.[104–107]

Fifth, since alcohol is a leading fetal neurotoxin, there needs to be a plausible biological explanation(s) as to why alcohol exposure at low levels should be of benefit. By contrast, there are multiple proven causal mechanisms for harm from alcohol as outlined above. Finally, controlled animal studies which do not suffer from psychosocial confounding effects find negative effects of alcohol at low doses.[Eg.108]

What is one to conclude from the uncertainty about the effects of moderate alcohol exposure on pregnancy? The bottom line is that alcohol is firmly established as a leading cause of acquired intellectual disability. This need to prove safety to introduce a product, rather than prove harm to discourage use, is known as the precautionary principle. This principle is applied to pharmaceutical products in pregnancy, in which there would be a therapeutic indication for use (unlike the case with alcohol, which has no known nutritional or therapeutic value in pregnancy).

At present, reviews conclude there is no clear level of alcohol consumption during pregnancy which is known to be safe.[95,109] To prove safety would, in our opinion, require the highest standard of medical evidence, in the form of at least two randomized human clinical trials with a range of sensitive outcome indicators. To the extent such trials might well be deemed unethical by an institutional research review board, one might fairly wonder why sanctioning the use of alcohol in pregnancy based on non-randomized observational studies is anything less than unethical and potentially dangerous.

Even without applying the precautionary principle, however, this review identified ample evidence from studies with stronger designs (i.e. Mendelian randomisation and animal studies) of dose-response, positive associations between level of alcohol exposure and risk of a range of birth defects. While these may be slight or even uncertain in any individual case, the overall result from this research is clear, with significant implications over the life course, plus multiple plausible causal pathways have been identified.



At present, reviews conclude there is no clear level of alcohol consumption during pregnancy which is known to be safe.



4 Prevention strategies

Drinking among non-pregnant persons (both women or men), and/or prior to the time of pregnancy recognition (among women) is arguably the key driver of alcohol-related risk for pregnant mothers and their offspring.[22,28,29,109] Therefore, efforts to reduce problems related to alcohol-exposed pregnancies cannot be limited to pregnancy exclusively, but rather must embrace a comprehensive approach to prevent and reduce excessive alcohol consumption in the general population.

Fortunately, there are a number of effective public policies that can reduce excessive drinking (e.g., binge drinking) and alcohol-related harms in the general population, including among those of reproductive age. Principal among these are policies to increase the price of alcohol (e.g., through increased alcohol excise taxes, minimum pricing policies, wholesale and retail price restrictions), reduce the physical availability of alcohol (restrictions on the number of alcohol outlets, hours of sale, minimum age for purchase or possession of alcohol), and restrictions on alcohol marketing.[110,111]

There are also clinical strategies that can identify and assist persons who interact with healthcare systems. Screening can potentially identify those with risky alcohol use, but patients are often not asked about their alcohol consumption. Those who drink in risky ways but who do not have a mild-moderate-alcohol use disorder may benefit from brief counseling intervention, and those with severe use disorder should be referred for specialty treatment.

The strategies designed to prevent foetal

alcohol effects prior to pregnancy or pregnancy recognition can be of two general types: (a) general strategies involving consumption and specifically heavy consumption independent of specific attention to pregnancy and (b) strategies specifically directed at risk of drinking prior to pregnancy or pregnancy recognition most likely directed at men and women of fertile age.

4.1 General Strategies to Reduce Consumption and Heavy Drinking

Research has been undertaken to estimate the potential impact of general alcohol policies especially directed at heavy consumption for both women and men as well as potential alcohol-related foetal effects.

One US study demonstrated significant associations between strong alcohol policies and population drinking outcomes. They scored all states on the extent and quality of effective alcohol policy implementation taking account of alcohol pricing, availability restrictions, impaired driving and underage drinking laws. They concluded that a 10-percentage point increase in an alcohol policy implementation score was associated with 9% lower odds of binge drinking, consistently for men, women and for most age and race subgroups.[112]

4.1.1 *Price of Alcohol*

A primary strategy for decreasing alcohol consumption involves raising its retail cost, most often by increasing government taxes on alcohol or by imposing minimum alcohol prices. Zhang (2010)[113] examined state alcohol excise taxes, self-reported drinking during pregnancy, and infant health across all states in the United States from 1985 – 2002. The study found that the proportion of mothers younger than 24 years decreased for each one cent increase in alcohol taxes, by 16% points for beer, 2% for wine taxes and 1% for spirits. It was also found that the likelihood of low birth weight decreased by 1-2% for every one-cent rise in beer taxes, 0.2 – 0.3% points in wine taxes and 0.1% points in liquor taxes.

4.1.2 *Alcohol Availability and Outlet density*

Drinking level can be related to the opportunity to purchase and consume alcohol and limits on the number and concentration of alcohol outlets are a proven strategy for reducing alcohol consumption and related harms.[110,114] One study conducted within the Department of Economics, Uppsala University as part of a doctoral dissertation[115] examined the impact of increases in the number of retail monopoly alcohol stores by Systembolaget between 1982 and 1992 which was associated with relaxation in the eligibility rules for new stores in the population centre of the previously dry municipality. The study found that the pace of new establishment increased sharply and that opening of an alcohol store in study areas was associated with increases in infant mortality rates. These effects on mortality were strongest for male children, for children from low-income households and for children where the mother had below median years of schooling. Children were also more likely to be born prematurely (5%), and mothers of children born after a store opened were, on average, younger, less educated and more likely to smoke during pregnancy. The study concluded that increases in alcohol availability influenced infant mortality through changes in prenatal health as well as lower school grades for surviving children at age 15 years.[115]

Another Swedish study[116] examined the impact of a dramatic change in alcohol policy to regions of Sweden that occurred in 1967 and 1968. This involved the experimental introduction of access to strong beer for 16 to 20-year-olds when previously this had been prohibited. Children born to young mothers during this period were followed up for many years. It was found that, in comparison with a control region of Sweden that had been unaffected by the policy change, the affected cohort had substantially worse employment and educational outcomes as well as poorer cognitive and other skills determined by objective tests. It was also determined that chil-



Drinking level can be related to the opportunity to purchase and consume alcohol.

dren of young mothers during this period had a 26% increased risk of serious alcohol-related health problems later in life, a relationship that was not observed among children born to older mothers at that time who would not have been affected by the policy.

A study from Ontario, Canada[117] which specifically examined alcohol outlet density and birth outcomes found that alcohol outlet density was positively correlated with the percentage of mothers living in poverty and as single-parents. Mothers living in high alcohol density areas were also significantly more likely to drink during pregnancy.

Taken together, these studies provide strong evidence that population level policies which reduce alcohol availability can influence parental drinking behaviours and have major significance for the extent and impact of prenatal alcohol exposure throughout the lives of the affected children.

4.2 Prevention strategies targeting individual drinking patterns

A review by the World Health Organisation[118] identified 29 studies focusing on FASD prevention efforts among non-pregnant and pregnant women. Several studies showed the effectiveness of pre-conception interventions in bringing down the risk of exposure to alcohol during a pregnancy by reducing risky drinking, increasing the use of contraception, or both. The use of brief interventions for pregnant women can be effective among those who drink at higher levels, especially when their partners are included. Effective interventions included motivational interviewing, a focus on reducing drinking and on increasing contraception use, especially when located in sexual health clinics. There was, however, limited evidence for the effectiveness of using wider public health education approaches through campaigns.

Another review identified nine alcohol RCT studies of interventions to reduce alcohol use during pregnancy, finding positive results in four alcohol RCTs. Effective components of these were described as action planning, behavioural contracts, the provision of written materials, problem solving, feedback on behaviour, social support, information about health consequences, encouraging behaviour substitution, motivational interviewing and goal setting.[119]

Gronqvist et al (2016)[120,121] evaluated the introduction of alcohol screening and brief interventions in Swedish antenatal clinics. They concluded that the program, which was delivered by midwives, improved infant health measured by reduced prescription of pharmaceutical drugs by 8.4% and of hospitalizations during the child's first year of life by 7.5%. The effects were likely driven by reductions in maternal drinking after the first trimester and may have extended beyond the birth of the child. The program consisted of screening for risky alcohol consumption using the Alcohol Use Disorder Identification Test (AUDIT) instrument; using Motivational Interviewing (MI) techniques and referral to specialist treatment for those identified as having more severe problems.

A quasi-experimental study in Sweden investigated the effect of providing counselling to all parents-to-be about alcohol use when they registered with antenatal care clinics. The intervention group included 238 couples and the comparison group comprised 271 couples. The control group received information about the study and a booklet about pregnancy and alcohol, which was mailed to their residence. Most women (92%) stated that their partner's support to give up alcohol was important. About 40% of partners reduced their alcohol consumption but perceived that they received less social support for alcohol reduction than their pregnant partner. Two-thirds of women in the intervention group indicated that their antenatal care clinic was the most important source of information about alcohol and pregnancy, compared to only half in the control group. The authors concluded that involving partners in counselling about alcohol restriction during pregnancy was a useful health promotion strategy.[122]

92%

A quasi-experimental study in Sweden investigated the effect of providing counselling to all parents-to-be about alcohol use when they registered with antenatal care clinics. … Most women (92%) stated that their partner's support to give up alcohol was important.

4.2.1 Warning Labels and Other Policy Approaches

Prevention directed at women as well as men of potential parenting ages can be designed to increase understanding of the risks associated with alcohol consumption prior to as well as during pregnancy. A number of policies have been implemented including mandatory warning signs (MWS) in establishments licensed to sell alcohol and healthcare facilities, where pregnant women receive treatment. Policy provisions specify who must post warning signs, the specific language required on the signs, and where signs must appear. An early study in the U.S.[123] used time series analyses to examine the potential impact of a federally required pregnancy alcohol warning label. The study found that self-reported drinking during pregnancy by women with no previous birth significantly declined after the implementation of the warning label. Another study[124] found that mandatory warning signs were associated with lower odds of self-reported binge drinking by women of child-bearing age.

A study[125] of US state-level policies regarding alcohol use among pregnant women found that living in a state with mandatory warning signs was significantly associated with an increased risk of low birthweight and premature births, on the one hand, and of lower prenatal care utilization on the other. This was a complex study that attempted to control for multiple maternal- and state-level characteristics to evaluate eight different state-level policies, including both 'supportive' (e.g. priority treatment for pregnant women, prohibitions against criminal prosecution) and 'punitive' policies (e.g. compulsory reporting of drinking mothers to child protection services). The study found that both supportive and punitive policies were associated with worse outcomes in terms of birth complications and prenatal care utilisation. The authors commented that these unexpected and inconsistent findings may be due to the stigmatising effect that such policies can have on women and therefore deter them from seeking prenatal care. It is difficult to interpret such apparently significant results from large observational studies utilizing multiple comparisons simultaneously such as this. On the one hand, the study evaluated only the presence or absence of the policies considered and not the extent of their implementation. Furthermore, the introduction of policies addressing alcohol-related birth complications could be triggered by evidence of high rates of these in the first instance i.e. reverse causality may be responsible for the observed association.

4.2 Current National Clinical and Public Health Recommendations

In Scotland, Ireland, USA, Canada, Australia, and New Zealand, for example, current guidelines consistently advocate abstinence only, with no amount of alcohol thought to be safe at any time during pregnancy.[119]

The US guidelines, e.g., also indicate that alcohol can cause problems for a developing baby throughout pregnancy, and that all types of alcohol are equally harmful, whether they be beer, wine or spirits. The advice to avoid alcohol to prevent birth abnormalities is also extended in these guidelines to avoiding alcohol at times when a woman might become pregnant. This is important because it is not uncommon for women to become pregnant but remain unaware for up to 4 to 6 weeks. If a woman is drinking alcohol during pregnancy, it is never too late to stop. Because brain growth takes place throughout pregnancy, the sooner a woman stops drinking the safer it will be for her and her baby.[126]



The advice to avoid alcohol to prevent birth abnormalities is also extended in these guidelines to avoiding alcohol at times when a woman might become pregnant. This is important because it is not uncommon for women to become pregnant but remain unaware for up to 4 to 6 weeks.



5 Postpartum effects

5.1 Introduction

Breastfeeding is universally recognised as the best option for optimising infant health, growth and development.[127] Breastfeeding is associated with better physiological and psychological outcomes for children including higher infant survival rates and better growth, healthy cognitive and neurological functioning[128,129] and facilitation of the mother-child bond that forms the basis of long-term psychological health.[127] Guidelines in many countries and the World Health Organisation recommend that mothers breastfeed exclusively for at least the first six months of life and continue until two years of age, introducing solid foods as appropriate.[127]

Several studies report that the majority of mothers avoid alcohol during pregnancy but that a large proportion re-start shortly following delivery[130,131], most often infrequently and at low levels.[132] Haastrup et al for instance estimated that about half of all nursing women living in Western nations are exposed to alcohol while breastfeeding and about half of those will breastfeed for 12 months or more.[133] There is some evidence that most women who drink while breastfeeding take steps to reduce alcohol exposure to their babies e.g. scheduling drinking around feeding times.[130,131,134]

Few studies report the prevelance and levels of alcohol exposure among breastfeeding mothers. This review was unable to find specific prevalence estimates for Sweden. However, a 2016 Norwegian study reported that 3 months postpartum, 50% of women were consuming alcohol at low levels and by 6 months this had risen to 80%. Moreover, some 30% of breastfeeding Norwegian mothers drank more than five drinks on an occasion (binge drinking) during the first 6 months postpartum.[135] In the Netherlands, levels of alcohol exposure among breastfeeding mothers appears to be lower with self-reported use ranging between 19% and 22%.[136]

5.2 Infant alcohol ingestion through human breast milk (human milk)

A small water-soluble compound, alcohol readily passes through biological membranes and enters human breast milk (human milk) by passive diffusion. At low levels of ingestion, human milk will reflect maternal blood alcohol levels within less than an hour.[134] At moderate to high levels of maternal intake, alcohol concentration in human milk may be higher than in the mother's blood.[137] For an average woman, it takes about two hours from the start of drinking to clear one unit of alcohol from human milk. For two units of alcohol it will take about 4 hours to clear

50%

About half of all nursing women living in Western nations are exposed to alcohol while breastfeeding and about half of those will breastfeed for 12 months or more.

and so on. Human milk will be free of alcohol once the mother's blood alcohol has returned to zero, however, attempts to clear alcohol via expressing or 'pumping and dumping' does not speed up the process.[134]

Although alcohol concentration in human milk directly reflects the mother's blood alcohol concentration, blood alcohol levels reached by the infant are much lower than for the mother. This is due to the diluting effect of the infant's own body water. It has been argued that in all but the most extreme cases, blood alcohol levels achieved by infants exposed to alcohol through breastmilk are so low as to present no threat to health.[137,138] However, it is also the case that infants metabolise alcohol more slowly than adults due to their lower levels of alcohol metabolising enzyme (alcohol deyhydrogenase).[66] It is also notable that effects of alcohol have been observed on infant sleep and human milk production even at very low levels of maternal intake.[132] In addition, the threshold or possible stochastic effects of alcohol on epigenetic factors are not yet clear, and in a period of rapid cell division such effects might be amplified during subsequent growth and development.



There is no doubt that maternal alcohol exposure is associated with early cessation of breastfeeding.

5.3 Lactation effects and breastfeeding duration

Contrary to popular urban mythology, alcohol ingestion by nursing mothers does not increase milk supply[132] and infants may in fact drink significantly less human milk when it contains alcohol.[139,140] Some mothers report feeling more relaxed during nursing after consuming alcohol, however, lactation hormones are adversely affected to the extent that time to milk ejection is longer, yield is reduced[132,141] and milk odour may be altered.[139]

There is some evidence that low levels of maternal alcohol exposure (0.3 – 0.4 grams per kg body weight) may also interfere with mother-child interactions during feeding times including suboptimal latching on by the infant and maternal irritation and mild sedation.[141,142]

A review by Giglia (2010) concluded that there is no doubt that maternal alcohol exposure is associated with early cessation of breastfeeding. At three months post-partum, cessation of breastfeeding is more likely to be reported my mothers who drink at higher levels, including binge drinking. Mothers who abstain or drink at low levels are more likely to breastfeed for longer.[132]

5.4 Infant sleep

Most human studies of the effects of alcohol in human milk have been concerned with infant sleep. Even at low maternal doses (e.g. less than 0.3 grams per kg), alcohol can adversely affect sleep-waking patterns of breastfed infants. A systematic review concluded that it is well established that small amounts of alcohol have a direct but subtle effect on infant sleep patterning.[134]

5.5 Infant development

A systematic review by Giglia and Binns (2006)[134] and a subsequent update published in 2010[132], concluded that evidence for effects of alcohol in human milk on infant development is inconsistent. Nevertheless, studies are limited by ethical concerns and evidence typically arises from studies that have been confined to low levels of maternal alcohol exposure or animal experimental studies.

An Australian study found that at maternal exposure levels of less than 30 grams per day, small effects of between 4% and 5% on infant psychomotor development were detectable. At higher doses of 80grams or more per day (heavy drinking mothers) deficits of around 15% were found.[143] However, some ten years later the same researchers found no effects using a comparable study design.[144] A longitudinal study of over 5,000 Australian infants examined children who had been breastfed and those who had not to determine whether maternal alcohol exposure predicted cognitive abilities. The authors concluded that exposing infants to alcohol through human milk may cause small but significant cognitive deficits and that the negative effect of alcohol



on cognition increased as average maternal alcohol exposure increased. These deficits were observed among children at about 7 years of age but by eleven years the effect was no longer detectable for most children.[145] It has been suggested that observed deficits in motor development may result from sleep disruption arising from regular maternal alcohol exposure.[146]

A small observational study investigated the effects of maternal pulque consumption (a mildly alcoholic drink made from agave, also called 'American aloe') on growth rate of breastfed infants. Average maternal alcohol exposure during lactation was about 114 grams per week. Independent of alcohol exposure during pregnancy, infants of mothers with the highest pulque consumption had slower growth up to about two and a half years. Children of mothers who drank light to moderate amounts demonstrated higher growth rates than both abstaining and heavy drinking mothers but it is likely that level of pulque drinking was a proxy for other variables that influence growth and development such as nutrition and socioeconomic status.[147]

Experimental animal studies using lactating female mice fed alcohol have demonstrated effects on pup immune function[148] as well as neuronal loss and decreased myelination in pup cerebellums.[149]

5.6 Sudden Infant Death Syndrome (SIDS)

There is limited research on the specific effect of human maternal alcohol exposure while breastfeeding on SIDS. A review of studies on SIDS and a range of maternal risk factors including alcohol exposure, either during pregnancy, after birth, or on the day of the sudden



Alcohol exposure after delivery is either a direct or environmental risk factor for all forms of infant mortality.

death, concluded inconsistent results.[150]

Alcohol does, however, appear to be at least an indirect risk factor for SIDS, specifically via co-sleeping.[151] Using a case-control design of SIDS infants and controls, Blair et al (2014) for instance found that infants sleeping in the same bed next to a parent who had consumed more than two units of alcohol (>16 grams) were at very high risk of SIDS (18 times greater) compared to infants who slept independent of their parents.[152]

O'Leary et al (2013) used Alcohol Use Disorder diagnoses located in health records of mothers as a proxy for heavy alcohol use to investigate alcohol's effect on SIDS and non-SIDS related infant deaths. Infants likely to have been exposed to heavy alcohol due to their mother's diagnostic status had a 3 fold increased risk of SIDS and the risk was highest when the mother's diagnosis occurred within the year after pregnancy but not during pregnancy. Risk of infant death from causes other than SIDS was also increased when mothers had received a diagnosis of Alcohol Use Disorder within twelve months of delivery.[153] These findings support the conclusion that heavy maternal alcohol exposure after delivery is either a direct or environmental risk factor for all forms of infant mortality.

5.7 Traumatic injuries

Caring for infants is both time and energy consuming but also requires completing a number of complex tasks, including feeding, bathing, holding, changing and carrying. Little or no research has been undertaken specifically on the effect of drinking on parental ability to safely care for infants and other children and avoid harmful accidents and potential injury. However, alcohol effects on other situations in life when complex tasks must be undertaken, for example, driving, biking, cooking, and sporting events reduces individual ability to perform these tasks safely and skillfully. Thus, it is reasonable to be concerned about the increased risk of infant injuries when one or both parents has been drinking. Future research on this relationship is necessary.

5.8 Guidelines and recommendation for breastfeeding and alcohol

The current Swedish guideline for breastfeeding mothers states that: 'Alcohol has no positive effects on breastfeeding. According to current research, however, it involves no medical risks for the child if you consume moderate amounts of alcohol when you are breastfeeding, that is to say 1 – 2 glasses of wine or its equivalent 1 - 2 times a week. The amount of alcohol that the child can ingest with the milk is very small.'[154]

The Swedish recommendation for alcohol use during breastfeeding appears to be in line with those of other Nordic countries, Denmark, Finland and Iceland, which generally refer to limiting alcohol exposure or avoiding heavy use; Norway is the exception and recommends avoiding alcohol.[155]

However, national guidelines from many other countries expressly recommend abstinence during pregnancy and breastfeeding including for example, Australia, UK, Canada, France, Germany and Italy.[156–162]

6 Conclusions and recommendations

To meaningfully reduce and prevent problems stemming from alcohol-exposed pregnancies, there needs to be a recognition that the problem is not confined to pregnancy nor limited to women. Addressing alcohol-exposed pregnancies requires a shared responsibility of the society at large, policymakers, educators, health care providers, partners and among women as reflected in the following points:

- Adopting effective population-based strategies to reduce excessive drinking -- including policies to increase the price of alcohol, limit its physical availability, and reduce alcohol marketing -- are the most effective ways by which to reduce excessive drinking among those of reproductive age, including pregnant women. These population-based strategies should be accompanied by effective clinical and public health approaches to assist women who are already pregnant or planning to become pregnant.
- Persons planning a pregnancy who choose to abstain or follow the recommended guidelines (no more than ten standard drinks per week and no more than four standard drinks per occasion) will improve the probability of a healthy pregnancy outcome.
- Although most women plan to stop drinking when they become pregnant, the time to pregnancy recognition is variable and many pregnancies are unexpected. For persons of reproductive age who drink, following low-risk alcohol consumption guidelines is recommended for a variety of health-related reasons. Binge drinking (4 or more drinks per occasion) during pregnancy is clearly associated with risk to the fetus.
- It is safest to abstain from any alcohol consumption during pregnancy. This applies also to partners. If they choose to continue drinking they should do so within low-risk guidelines.
- Firm evidence on the effects of low alcohol consumption while breast feeding is lacking. But even low levels of ethanol exposure can disrupt infant sleep patterns and reduce maternal milk production. Applying the precautionary principle here would suggest it safest to avoid alcohol exposure while breastfeeding. However, consumption of 1 standard drink consumed 2 hours prior to breastfeeding is unlikely to result in significant blood alcohol concentrations in a nursing mother.
- Create a national competence center for FASD for ongoing epidemiological surveillance of estimates of alcohol consumption before, during and after pregnancy, and the prevalence of FAS and FASD. In addition the national centre could provide specialist assessment and treatment and training for relvant professionals.

Recent Swedish guidelines on low risk alcohol consumption state that while "less is better", for the reduction of alcohol-related harm in general, healthy men and women run a low risk of harm at a consumption of less than ten standard drinks per week. A standard drink in Sweden contains 12 grams of pure alcohol (ethanol) and is found in a small glass of wine (10 cl), a bottle (33 cl) of beer or a shot of spirits (3–4 cl). Binge drinking is always a risk and the recommendation here for men and women is not to exceed three standard drinks on any occasion.[163]

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