

Risks and guidelines for the consumption of alcohol during pregnancy

Ulrik Schiøler Kesmodel

Ulrik Schiøler Kesmodel, Department of Obstetrics and Gynaecology, Herlev University Hospital, 2730 Herlev, Denmark

Ulrik Schiøler Kesmodel, Institute for Clinical Medicine, University of Copenhagen, 2200 Copenhagen N, Denmark

Author contributions: Kesmodel US performed the literature search and wrote the paper.

Conflict-of-interest statement: The author declares no conflict of interest for this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Ulrik Schiøler Kesmodel, Professor of Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, Herlev University Hospital, Herlev Ringvej, 2730 Herlev, Denmark. ulrik.schioeler.kesmodel@regionh.dk
Telephone: +45-3868-1612

Received: June 28, 2015

Peer-review started: July 5, 2015

First decision: September 17, 2015

Revised: November 13, 2015

Accepted: January 21, 2016

Article in press: January 22, 2016

Published online: May 10, 2016

Abstract

Daily average intake of alcohol during pregnancy has consistently been associated with short term adverse outcomes such as miscarriage, preterm birth and intrauterine growth restriction, a large variety of malformations, as well as long term adverse outcomes

such as foetal alcohol syndrome, mental retardation and general impairment of cognitive functions including intelligence, attention, learning abilities as well as social and behavioural functions. Weekly average consumption and alcohol binge drinking (usually defined as ≥ 5 drinks on a single occasion) independently of high daily average intake has not been consistently associated with short and long term adverse outcomes. Health authorities in most countries recommend that pregnant women completely abstain from alcohol. Even so, many health professionals including doctors, midwives and nurses do not provide information to pregnant women in accordance with the official recommendations, although a large proportion of women of child bearing age and pregnant women drink alcohol, especially before recognition of pregnancy. The discrepancy between guidelines and the information practice of health personnel is likely to continue to exist because guidelines of abstinence are not clearly evidence-based and not in line with current focus on autonomy and informed choice for patients, and because guidelines do not consider the everyday clinical communication situation.

Key words: Alcohol; Binge drinking; Pregnancy; Adverse pregnancy outcomes; Neuropsychological development

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Daily average consumption of alcohol during pregnancy has been systematically associated with short and long-term adverse outcomes, while lower weekly average consumption and alcohol binge drinking independently of high daily average intake has not. Health authorities in most countries recommend that pregnant women abstain from alcohol. Even so, many health professionals do not provide information to pregnant women in accordance with the official recommendations. The discrepancy between guidelines and the information practice of health personnel is likely to continue, because guidelines of abstinence are not clearly evidence-based

and not in line with current focus on patient autonomy.

Kesmodel US. Risks and guidelines for the consumption of alcohol during pregnancy. *World J Obstet Gynecol* 2016; 5(2): 162-174 Available from: URL: <http://www.wjgnet.com/2218-6220/full/v5/i2/162.htm> DOI: <http://dx.doi.org/10.5317/wjog.v5.i2.162>

INTRODUCTION

It has been known for thousands of years that alcohol consumption may compromise human reproduction and harm the newborn baby. In his *Problems*^[1], Aristotle described how alcohol may reduce semen quality and male potency ["...semen of drunkards (is) generally not reproductive..."]. In his *History of Animals* he described how breast milk from wine-drinking women may cause convulsions in the weaning baby^[2]. During the first half of the 18th century, during the English gin epidemic, the English College of Physicians asked Parliament to re-introduce control with the distillation process, because gin was "a cause of weak, feeble and distempered children"^[3].

Some one hundred years later a movement had been set in motion that called on women not to drink alcohol while pregnant or while breast-feeding, for as Aristotle had suggested, "alcoholic milk" might cause convulsions in the newborn^[4], and children nursed on abstinence on the other hand escaped many common childhood disorders^[4].

In 1848, a population based survey was carried out among 574 intellectually disabled people in Massachusetts, United States. Approximately half of the intellectually disabled people (then termed idiots) had parents who were "habitual drunkards"^[5].

In 1899, in England, Sullivan^[6] described 120 chronic alcoholic women in Liverpool Prison or their relatives and their approximately 600 children. Approximately one in ten children was stillborn, and 56% of the children had died within two years after delivery, usually because of convulsions. The longer the mother had been drinking the greater the risk. But if the mother was abstinent during imprisonment, the child's chance of survival was increased^[6].

By the beginning of the 20th century, alcohol consumption during pregnancy had also been associated with miscarriage, malformations and preterm birth^[3].

During the American Prohibition of the 1920s and 1930s alcohol was less accessible, and following the Prohibition the potentially damaging effects of alcohol consumption during pregnancy was hardly an issue. In fact, in the late 1960s and 1970s, a number of case series (inherently lacking a reference group) - mainly from the New York Hospital - even suggested that infusion of alcohol could potentially prevent preterm birth in women with threatening preterm delivery^[7], although others had difficulties replicating these findings^[8]. In

1975, a paper was published including several comparison groups, showing that the therapeutic effect of alcohol on preventing premature labour was no better than that obtained with placebo^[9].

In retrospect, it is interesting that while experiments were being carried out using alcohol infusions as a treatment among pregnant women and published in high profile journals^[7], the first modern description of the potentially harmful effects of high intake of alcohol during pregnancy was published in French and went almost unnoticed^[10]. In fact, today's focus on the damaging foetal effects of high alcohol intake during pregnancy was started with the (re-) discovery of the Foetal Alcohol Syndrome (FAS) in 1973^[11].

The aim of this paper was to assess the potentially damaging effects of alcohol intake during pregnancy at all intake levels, the attitudes and knowledge among pregnant women and health personnel towards the issue, drinking patterns, and how official recommendations are handled in everyday clinical practice by health personnel.

METHODOLOGY

A systematic literature search in PubMed was performed for each of the topics: Foetal/fetal damage, attitudes and knowledge, drinking patterns, and recommendations. Search terms may be obtained from the author. All identified records were screened for eligibility by article title. Abstracts were read if the study appeared to be relevant for inclusion. Full text of all cited papers were read. The computerized literature search was supplemented with a hand-search of the bibliography of all included papers. The study selection was done by the author.

A brief introduction to measurement of alcohol intake during pregnancy

A single measure of overall consumption does not necessarily give a sufficient picture of the actual pattern of consumption: Patterns of alcohol consumption are often complex, and much too often alcohol consumption is categorised in an oversimplified manner. In clinical and scientific practice, the alcohol consumption pattern of an individual is usually described by three components: Frequency, quantity, and variability^[12], and a fourth component is now being assessed in more and more studies: Timing^[13]. Most often a measure of the average number of standard drinks per day or per week at a more or less well-specified point in time during pregnancy is provided (measuring frequency and quantity, *i.e.*, the number of drinking episodes \times the number of standard drinks on each episode). Many attempts have been made to include a measure of variability into measures of quantity and frequency, creating a quantity-frequency-variability measure^[12]. Variability is often measured as binge drinking, usually defined as intake of ≥ 4 or ≥ 5 drinks on a single occasion. Binge drinking is incorporated into many of

these measures and indices. Binge drinking, however, is now often used as a separate exposure and timing of such episodes may be of importance.

Other aspects of alcohol consumption such as context (setting, *i.e.*, private vs public, *etc.*), unit size and type of alcohol are scarcely reported. However, the potentially harmful effects of alcohol on the foetus are most likely caused by ethanol itself, and hence the type of alcohol is unlikely to be of any importance, as suggested in some studies^[14].

No reliable or valid biomarkers of alcohol intake during pregnancy have been found.

THE DAMAGING EFFECTS OF ALCOHOL DURING PREGNANCY - WHAT IS THE CURRENT EVIDENCE?

Average alcohol intake

FAS is a diagnostic entity with fairly well defined diagnostic criteria^[15], but even so diagnostic criteria differ somewhat and the diagnosis may be difficult^[16]. Confirmed prenatal alcohol exposure is not required to make a diagnosis, but all three of the following findings are required, although some differences in diagnostic criteria are observed within each category^[15,16]: (1) Documentation of at least 2^[16] or all 3^[15] of the following facial features (smooth philtrum, thin vermilion border, and small palpebral fissures); (2) Documentation of growth deficits (Confirmed, age, sex, gestational age, and race or ethnicity adjusted prenatal or postnatal height or weight, or both, at or below the 10th percentile, documented at any one point in time); (3) Documentation of CNS abnormality [I : structural (small head circumference or brain abnormalities observable through imaging)^[15,16], II : neurological (not due to a postnatal insult or fever)^[15], or III : functional]^[15]. Functional deficits may be either global cognitive or intellectual deficits representing multiple domains of deficit with performance below the 3rd percentile (2 standard deviations below the mean for standardized testing); or functional deficits below the 16th percentile (1 standard deviation below the mean for standardized testing) in at least three of the following domains: (1) cognitive or developmental deficits or discrepancies; (2) executive functioning deficits; (3) motor functioning delays; (4) problems with attention or hyperactivity; (5) social skills; and (6) other, such as sensory problems, pragmatic language problems, or memory deficits.

Apart from the diagnostic features mentioned above, FAS has been associated with a huge number of malformations, which are not specific for FAS, but still may be caused by the excessive, high average daily alcohol intake, *e.g.*, craniofacial such as microcephaly, ptosis, retrognathia, micrognathia/flat midface, maxillary hypoplasia, and short upturned nose; skeletal such as pectus excavatum, joint defects, radioulnar synostosis, hypoplastic fingernails and toenails; cardiac such as atrial- and ventricular septal defects; cleft

lip and/or palate; ocular defects including myopia, strabismus and microphthalmia; dental such as dental malocclusion, hypoplastic/misaligned teeth and faulty enamel; hypospadias, hypoplastic/dysplastic kidneys and inguinal hernia^[16-19].

FAS represents the severe end of the Foetal Alcohol Spectrum Disorders (FASD), a widely used term for a group of at least three types of conditions^[16,20]: FAS, Alcohol-Related Neurodevelopmental Disorder (ARND), and Alcohol-Related Birth Defects (ARBD). Some have attempted to define ARBD (malformations) as a diagnostic entity including confirmed maternal alcohol exposure, ≥ 2 facial features as mentioned above, and a combination of structural defects/malformations^[16], although this is not universally acknowledged. FASD and ARND (*e.g.*, intellectual disabilities, learning and behaviour problems), are umbrella terms and are not at this point diagnostic entities^[15,16]. Some also include partial FAS as an additional entity^[16].

FAS and all the characteristics associated with it is by definition caused by (high average daily) alcohol intake during pregnancy. To the extent that smaller amounts of alcohol are potentially harmful, the effects are likely to be the same but smaller.

Anthropometric measures and growth: A recent meta-analysis assessed the association of average alcohol consumption with low birth weight and being small for gestational age (SGA)^[21]. The meta-analysis suggested a non-linear association^[21]. The meta-analysis is interesting for several reasons: In an analysis of any alcohol use vs no alcohol use, including a total of 28 studies, alcohol users were at increased risk of having children with low birth weight (RR = 1.12, 95%CI: 1.04-1.20). Not surprisingly, studies with no confounder control (12 studies) showed a higher increased risk (RR = 1.27, 95%CI: 1.00-1.61), while studies adjusting for potential confounders (17 studies) showed an insignificantly increased risk of low birth weight (RR = 1.06, 95%CI: 0.99-1.13). The pooled odds ratio of SGA in all studies (11 studies) was 1.11 (95%CI: 0.95-1.30), and in studies that adjusted for confounders it was 0.99 (0.89-1.10).

However, looking at any alcohol intake, does not distinguish between low and high alcohol intake. In the study, meta-regression was carried out using linear as well as first-order and second-order fractional polynomial regression. For both low birth weight and SGA polynomial regression fitted the data better than linear regression. Intake of less than one drink a day on average showed no association with poor outcome, whereas intake of more than one drink per day on average was associated with a steadily increasing risk of low birth weight up to approximately 10-12 drinks per day (RR = 7.48, 95%CI: 4.46-12.55)^[21].

Preterm birth

The same meta-analysis showed data on preterm

birth^[21]. In an analysis of any alcohol use vs no alcohol use, including a total of 21 studies, alcohol users were not at increased risk of preterm birth (RR = 1.03, 95%CI: 0.91-1.16). Studies adjusting for potential confounders (11 studies) yielded an attenuated estimate (RR = 0.93, 95%CI: 0.86-1.01). Again, for preterm birth, polynomial regression fitted the data better than linear regression. Intake of less than 1½ drinks a day on average showed no association with preterm birth, whereas intake of more than 1½ drinks per day on average was associated with a steadily increasing risk of preterm birth with increasing alcohol intake. For women drinking three drinks per day on average, the risk of preterm birth was 23% more likely than in nondrinking mothers (RR = 1.23, 95%CI: 1.05-1.44)^[21].

In general, the relative risks, but not necessarily the differences between the two risk estimates, for very preterm birth (before 32 wk of gestation) are higher than the relative risks for moderate preterm birth (32-36 wk of gestation)^[14]. Mode of delivery does not seem to affect the risk^[22].

Foetal death - spontaneous abortion and stillbirth

From a methodological point of view, spontaneous abortion is perhaps one of the most difficult pregnancy outcomes to assess, especially in the first trimester. To mention but a few: Variation in self-testing behaviour, *i.e.*, variations related to the different gestational ages at which different women choose to perform a pregnancy test - women testing themselves very early in pregnancy will appear to have higher abortion rates than women who do not^[23]. Very early spontaneous abortions (*i.e.*, weeks 0-6) are usually not recognized, and hence these are not included in studies on spontaneous abortions. Most studies apply logistic regression analysis, and they will therefore tend to overestimate the risk of early spontaneous abortions because the odds ratio will overestimate the true risk ratio. This problem may be dealt with by applying survival analysis techniques with delayed entry or left truncation, so that women do not inappropriately contribute time at risk before recognition of pregnancy^[23]. Survival analysis also allows pregnancies that end in induced abortion to contribute time at risk to the analyses, since such pregnancies are also at risk of spontaneous abortion until the day of the induced abortion^[23]. Only few studies have previously addressed this problem by using Cox proportional hazard models with delayed entry^[24-26].

Increased risk of early spontaneous abortion has been reported in alcoholics^[27,28]. At lower intake levels, some studies show no association^[29-33], while most studies seem to suggest an increased risk of first trimester spontaneous abortion with an intake of ≥ 1 drink/d on average^[34-36]. Two studies with open ended high intake group of > 3 ^[25] and ≥ 5 ^[24] drinks/wk on average, respectively, suggested an increased risk within this group, but because of the open ended categorization it is unclear at what level the actual effect

increases.

A recent (and much cited) study showed an increased risk of first trimester spontaneous abortion at intake levels of 2-3½ drinks/wk on average (Hazard ratio = 1.66, 95%CI: 1.43-1.92)^[26]. As for second trimester spontaneous abortions, the majority of studies show no association, although two studies showed an increased risk at an intake of ≥ 1 drink/d on average^[35,36]. Again, a recent study showed an increased risk of very early second trimester spontaneous abortion (weeks 13-16) at intake levels of 2-3½ drinks/wk on average (Hazard ratio = 1.57, 95%CI: 1.30-1.90)^[26].

Interestingly, the authors of the one study showing an association between average intake levels of 2-3½ drinks/wk on average and first and early second trimester abortions, found hardly any association between alcohol binge drinking and spontaneous abortion, as mentioned below^[37]. It seems biologically implausible that in the same population 2-3 drinks/wk on average should increase the risk, while intake of ≥ 5 drinks on a single occasion does not.

The definition of stillbirth differs between studies, with gestational age usually varying between ≥ 22 wk or ≥ 28 wk of gestation. In most studies, the rate of stillbirth has ranged between 3 and 6 per thousand^[26,38]. While children of alcoholics are probably at increased risk of stillbirth^[28], in the majority of studies no association or even a slightly increased risk among abstainers compared with women with low intake has been described^[26,38]. One study with an open-ended high intake group of ≥ 5 drinks/wk on average has suggested an increased risk within this group^[39].

Malformations

As mentioned above, FAS has been associated with a large number of malformations in different parts of the body. Similar malformations have been described in children of alcoholics without other signs of FAS. At lower intake levels, intake of ≥ 3 drinks/d on average has been associated with craniofacial and genitourinary malformations^[40,41], and intake of $\geq 1-2$ drinks/d on average has been associated with musculoskeletal malformations and malformations of the sex organs and inguinal hernias^[40,42]. A single study has shown increased risk of cryptorchidism among boys of women reporting intake of ≥ 5 drinks/wk on average, with increasing risk up to ≥ 9 drinks/wk on average^[43]. Unfortunately, no estimate was reported separately for the 5-8 drinks/wk group, making it unclear where the actual effect started. One study, using different assessments of alcohol consumption, suggested a possible threshold for the risk of malformations. Although different measures yielded different thresholds, the lowest level at which an effect was observed was 0.5 ounces/d on average corresponding to approximately 1 drink/d on average^[44].

While timing of alcohol consumption is likely to be an important issue when assessing the risk of malfor-

mations, few studies have studied this aspect.

Neuropsychological development

Daily average intake of alcohol during pregnancy may affect intelligence^[45,46]. IQ may be reduced by up to 25 IQ points in children of alcoholics compared to children of women with no or very limited intake, whereas intake of 2-4 drinks/d on average may reduce IQ by 5-7 IQ-points^[47,48].

Executive functions^[49,50] and attention deficits in children are among the most commonly reported effects of daily drinking during pregnancy^[51-53]. It has been suggested that the attention deficit potentially caused by high prenatal alcohol exposure may constitute a specific subtype of Attention Deficit Hyperactivity Disorder^[54]. Cerebral structural changes after prenatal alcohol exposure have been observed in several areas considered to be involved in attention processes^[55].

Daily average prenatal alcohol exposure has also been associated with deficits in, e.g., speed of information processing^[56], memory^[52], learning^[57], spelling, and behaviour^[57]. Children of alcoholics have also been reported to have more psychiatric and psychopathological symptoms^[58].

Based on > 30 studies a recent systematic review showed that among studies reporting maternal intake of more than four drinks per day on average, only one study showed no effect on motor function, while among all studies reporting intake levels of less than 10 drinks/wk on average, only one study showed deficits^[59] in gross and fine motor function. Intake of 1-7 drinks/wk on average was not associated with such deficits^[59].

In a recent meta-analysis, the association between average alcohol intake of 0 - ≤ 6 drinks per week on average and neuropsychological development was assessed as follows: (1) > 0 - ≤ 3 drinks per week and visual and motor function, cognition, behaviour, language and verbal function; (2) 3- ≤ 6 drinks per week and visual and motor function, attention, cognition, behaviour, language and verbal function; and (3) > 0 - ≤ 6 drinks per week and visual and motor function, cognition and behaviour was evaluated^[60]. Overall, no significant associations were observed between any of the exposure categories and the included neuropsychological outcomes (*i.e.*, visual and motor function, attention, cognition, behaviour, development, and language skills). When restricting analyses to studies of high quality (as determined by Newcastle-Ottawa-assessment-scale score), two significant results appeared, one showing a negative and one showing a positive effect: Three studies with approximately 11900 children aged 9 mo to 5 years yielded a statistically significant detrimental association between intake of 3 - ≤ 6 drinks per week on average and child behaviour ($P = 0.01$)^[60], while 7 studies with approximately 26100 children, yielded a small, statistically significant, beneficial association between intake of > 0 - ≤ 6 drinks per week on average and child cognition ($P =$

0.03). It should be noted that cognition was measured by different IQ-tests in three studies (WPSSI-R, WISC, Raven), the Bayley Scales, Mental Development Index, in three studies, and the Bracken School Readiness Assessment in one study^[60].

It is possible, however, that the effect of alcohol on child IQ may be modified by genetic predisposition^[61], but very little evidence on this issue has been published. A recent study on behaviour not included in the meta-analysis showed no effect of average weekly intake of alcohol on behaviour in 5-year-old children^[62].

In conclusion, average daily intake of alcohol during pregnancy has been associated with intrauterine growth restriction, preterm birth, foetal death throughout pregnancy, malformations, poor neurocognitive development and may cause deficits in psychomotor function, attention, memory, executive function, intelligence, behaviour and learning. However, less than average daily average consumption has not been systematically associated with any of these outcomes. With respect to early spontaneous abortion, however, the many methodological problems inherent in such studies should warrant caution in the interpretation of the results. Overall, the results suggest that if any, the potential effect of average weekly alcohol consumption is likely to be small.

BINGE DRINKING INDEPENDENTLY OF HIGH DAILY AVERAGE INTAKE

Pregnancy and birth outcomes: The risk of foetal death in clinically recognized pregnancies has been assessed in one study^[37]. Binge drinking, including number of binge episodes and timing of binge drinking, was not associated with overall risk of foetal death or risk of miscarriage in the first or early second trimester (until pregnancy week 21)^[37]. Women reporting ≥ 3 binge episodes had an increased risk of stillbirth (week 22 or later, OR = 1.56, 95%CI: 1.01-2.40), but timing of binge drinking was not associated with stillbirth^[37].

Few studies have assessed the association between alcohol binge drinking and anthropometric measures: In studies adjusting for potential confounders, no significant or clinically relevant associations were described between binge drinking and weight, length or head circumference at birth^[63-67]. Only two studies reported an adjusted difference in birth weight, respectively -41 g 95%CI: -92; 10^[65] and -41 g 95%CI: -108; 27 for ≥ 2 binge episodes^[67]. The remaining studies either did not show the adjusted results^[63,66], or showed no measures of association, but simply stated that no differences were observed^[64]. Number of binge episodes was not associated with anthropometric measures^[67], while timing of binge drinking has not been reported.

Few studies, mainly of poor quality, have assessed birth defects including features of FAS^[68]. One study reported that newborn children of binge drinkers had slightly shorter palpebral fissures, but no association

was reported with other facial features^[69]. Two subsequent studies not included in the above systematic review^[68] showed no association between binge drinking and cryptorchidism^[43] or between number or timing of binge episodes and congenital heart defects, in particular atrial and ventricular septal defects^[70].

A systematic review of the effects of alcohol binge drinking suggested that prenatal binge drinking might be associated with impaired neurodevelopment^[68]. Based on five studies with different definitions of binge drinking, another systematic review concluded that the issue of whether prenatal alcohol binge drinking was potentially associated with motor dysfunction in children was unsettled^[59].

These issues were updated in a recent meta-analysis including nine outcomes (visual and motor function, attention, memory, executive function, cognition, behaviour, language and verbal, academic reading performance, and academic math performance)^[60]: When including all eligible studies irrespective of quality, a significant detrimental association between binge drinking and child cognition was observed (Cohen's d -0.13; 95%CI: -0.21, -0.05). The analysis included 8 studies on children aged 6 mo to 14 years. However, the results of this meta-analysis were no longer significant when limited to data from studies of high quality^[60]. Analyses of motor function (6 studies), executive function (3 studies), attention (3 studies) and behaviour (5 studies) showed no significant or clinically relevant associations^[60].

In conclusion, prenatal alcohol binge drinking independently of high, average daily intake does not seem to be systematically associated with short or long term adverse outcomes to a clinically relevant degree. However, timing of binge drinking is not well studied.

RECOMMENDATIONS

Official recommendations and guidelines from health authorities are meant to guide clinical practice and health behaviour among patients and the population at large. Many guidelines and recommendations are based on scientific evidence, but evidence evolves and changes over time, and the interpretation of the evidence may vary depending on the cultural setting. For example, the Gin Epidemic in England was following by a petition to Parliament to more strict control with the distillation process, while the Prohibition in the United States was followed by direct denial that alcohol during pregnancy might be harmful^[3].

OFFICIAL RECOMMENDATIONS

In the 1990s, health authorities and health professionals in most countries recommended that pregnant women should abstain from alcohol during pregnancy^[17,71-73]. However, in some countries, recommendations on alcohol during pregnancy have changed considerably over the past two decades.

In Australia, for example, the 1992 guidelines

suggested that pregnant women should abstain from alcohol^[73]. However, the 2001 guideline modified this view to suggest that while pregnant women should consider not drinking at all and should never become intoxicated, "if they choose to drink, over a week, should have less than seven standard drinks, and, on any one day, no more than two standard drinks"^[74]. Two years before, in 1999, a comparable recommendation was issued by the Danish Health and Medicines Authority (previously Danish National Board of Health): "Avoid alcohol in pregnancy if possible; if you drink, drink no more than one drink per day; do not drink every day"^[75]. In the United Kingdom, the recommendation from the Department of Health suggested that intake of up to 1-2 United Kingdom units once or twice a week may be acceptable.

In 2007, the Danish Health and Medicines Authority again changed its recommendation to: "If you are pregnant: Avoid alcohol. If you are trying to conceive: Avoid alcohol, to be on the safe side"^[76]. Around the same time, a draft guideline was made available in Australia, leading to the 2009 guideline: "not drinking is the safest option"^[77]. Only in the United Kingdom, the Department of Health and National Institute for Health and Clinical Excellence and RCOG still condone low levels of alcohol intake (as of November 2015): "Women who are pregnant or trying to conceive should avoid alcohol altogether". However, if they do choose to drink, to minimize the risk to the baby, we recommend they should not drink more than 1-2 units once or twice a week and should not get drunk"^[78,79].

ACTUAL RECOMMENDATIONS FROM HEALTH PROFESSIONALS

While health authorities in most countries recommend abstinence from alcohol during pregnancy, little is known about the actual information practice of health professionals.

Doctors

In 2002-2003, in Australia, a postal survey among health professionals showed that only 57%-67% of general practitioners and obstetricians routinely asked pregnant women about alcohol use^[80]. The complex recommendation (consider not drinking/do not become intoxicated/have < 7 drinks over a week/on any one day have no more than 2 standard drinks) was provided in its entirety by only 5% of obstetricians and 17% of GPs^[80].

A Danish study among GPs in 2000 and 2009 showed that in 2000, when a complex recommendation was used, only 5% spontaneously mentioned all three statements that made up the recommendation (avoid alcohol in pregnancy/if you drink, drink no more than one drink per day/do not drink every day) and 26% explicitly said they did not know the recommendation. In 2009, when the recommendation had been

Table 1 Potential advantages and disadvantages of recommending abstinence vs a more condoning approach

	Abstinence	Condoning approach
Advantages	Simple message No alcohol = no alcohol induced adverse effects Safest choice considering potential uncertainties related to interpretation of the scientific evidence	Little evidence that a low intake is harmful
Disadvantages	Little evidence that a low intake is harmful May cause guilt in women who have been drinking a few drinks, especially in early pregnancy What are health professionals going to tell women who have been drinking a few drinks, especially in early pregnancy? Disagreements between health authorities and health professionals may lead to confusion and worry among pregnant women	Complex message To regard recommendations as guidance rather than an absolute limit may increase alcohol consumption among pregnant women May be regarded as guidance rather than an absolute limit Alcoholics may have difficulties stopping after intake of only small amounts

changed into complete abstinence, 87% knew the new recommendation. Even so, only 53% recommended abstinence to pregnant women in 2009^[81].

The fact that many doctors do not provide information to pregnant women in accordance with the official recommendations seems to be in accordance with the attitudes of many doctors. American gynaecologists have been shown not to consider a mean intake of 4-5 drinks/wk to be harmful^[82], and only 51% of Danish GPs believed that pregnant women should completely abstain from alcohol^[81].

Midwives and community nurses

Danish midwives have reported attitudes and information practice comparable with GPs: Thus, in 2009, only 46% recommended abstinence, even though more than 90% knew the official recommendation of abstinence, and only 48% believed that pregnant women should completely abstain from alcohol^[83]. Among Australian community nurses caring for pregnant women 41% reported routinely asking about alcohol use^[80].

ARGUMENTS FOR AND AGAINST DIFFERENT RECOMMENDATIONS

Some of the advantages and disadvantages of recommending abstinence vs a more condoning approach are listed in Table 1.

A general recommendation about alcohol intake during pregnancy may be based on two different arguments, both based on the existing literature^[75]: (1) essentially, intake of small amounts of alcohol has not been consistently associated with adverse effects; (2) It has not been proved that intake of small amounts of alcohol in pregnancy is not harmful, hence pregnant women should abstain from alcohol - or as it is often phrased: No safe level of alcohol consumption has been established.

A recommendation of abstinence is based on the latter argument. However, most scientific studies are based on the (statistical) hypothesis that intake of small amounts of alcohol are not harmful to the foetus. But

a hypothesis of no harm can never be proved, as it is impossible to prove that something does not exist.

ALCOHOL DRINKING AMONG PREGNANT WOMEN

Drinking patterns

Alcohol consumption among women of child bearing age is often high. This is concerning since many pregnancies are unplanned^[84]. In the United Kingdom, approximately 85% of women of child bearing age drink alcohol^[85], and in Denmark, Norway and Sweden as many as 89%-95% of pregnant women admit to drinking alcohol before pregnancy^[86-88]. In the United Kingdom, the average consumption of women aged 16-44 years was approximately 10-11 drinks/wk in 2011^[89], virtually unchanged since 2007^[85]. In the United States, binge drinking prevalence (28.2%) and intensity (9.3 drinks per occasion) has been reported to be highest among persons aged 18-24 years^[90] and this is in line with a general observation that, e.g., college students in many countries report particularly high intake^[91]. In Sub-Saharan Africa ten countries are among the 22 countries worldwide with the highest increase in per capita alcohol consumption in the recent years^[92]. While the proportion of female abstainers is generally high in this region, the proportion of binge drinkers is high^[92].

Even so, most people who binge drink are not alcoholics or alcohol dependent^[93].

Among pregnant women, reported consumption is considerably lower, but with huge variation from one country to another. In Denmark and Norway, 85%-90% of pregnant women have been reported to reduce alcohol consumption after recognition of pregnancy^[86,87].

In a Danish study, approximately 70% of pregnant women admitted to drinking alcohol during the second trimester, i.e., after recognition of pregnancy^[86]. Even so, the actual consumption level was low with an average of 1 drink/wk, and 92% of the women reported a maximum intake of 3 drinks/wk^[86], comparable to a report from Sweden^[88]. Approximately 1% admitted to drinking ≥ 7 drinks/wk^[86]. In Norway, only 23%

report alcohol consumption after pregnancy week 12^[87], comparable to new Danish data on current levels of alcohol intake, and in the United States, 15% reported any alcohol consumption, including 3.5% who admitted to either intake of ≥ 7 drinks/wk or binge drinking^[94].

Interestingly, while 25% in Denmark reported intake of 2 or more drinks on a single occasion in the 2nd trimester in the late 1990s^[86] none did so in Sweden^[88].

Interestingly, new up-to-date information on prevalence of alcohol consumption is difficult to find.

In Denmark, approximately 50% of pregnant women admit to alcohol binge drinking during pregnancy^[12,86]. The majority do so before recognition of pregnancy with a peak in week 3 after the last menstrual period around the time of ovulation, and hence around the time of conception for most women^[12]. In Norway, 25% admit to binge drinking in weeks 0-6, *i.e.*, before recognition of pregnancy^[87]. In the United States, only 3% have previously admitted to binge drinking during pregnancy^[95].

There may be several explanations for these differences. As opposed to studies investigating the association between an exposure (*e.g.*, alcohol consumption) and adverse outcomes^[96], analyses of prevalence of consumption are likely to be much more influenced by selection bias. For example, the above study showing that nearly 70% of pregnant women drink alcohol during pregnancy, and that 50% binge drink in early pregnancy, was based on a sample of 92% of eligible pregnant women^[86]. A large, prospective cohort study from the same period showed that only 27% of pregnant women in Denmark reported binge drinking in early pregnancy^[97], but the participation rate was lower, approximately 30%^[97,98]. While the former study used personal interviews the latter used telephone interviews, but the questions on binge drinking were essentially identical. Hence, the discrepancy in proportions of binge drinkers was most likely due to selection bias. Previous studies have suggested a North-South difference in drinking pattern in Europe, but especially among young (non-pregnant) people, this difference is diminishing^[99]. Therefore, reported differences in consumption patterns should be interpreted with great caution.

CHARACTERISTICS OF ALCOHOL DRINKERS DURING PREGNANCY

With a view to identifying alcohol drinkers during pregnancy, only few studies have attempted to assess risk factors associated with average alcohol intake and binge drinking during pregnancy^[86,94,95,100].

Even so, the pattern of risk factors is fairly consistent across different populations: Smoking and being single are consistent risk factors for high average alcohol intake, while employment and high income are less consistent findings^[86,94]. Consistent risk factors for binge drinking are smoking and being single^[86,95,100]. Nulliparity and employment/high income are less

consistent findings^[86,95,100]. One study has assessed risk factors for binge drinking before and after recognition of pregnancy and found somewhat different patterns^[100]: Age 25-29 years, nulliparity, ≤ 12 mo's time to achieve a pregnancy, late recognition of pregnancy at week 6 or later, being a lower grade professional compared to being unskilled or unemployed, smoking, being single and some average alcohol intake were risk factors in the period before recognition of pregnancy. Multiparity, overweight and obesity, unplanned pregnancy, early recognition of pregnancy, self-reported mental disorders, smoking, being single and some average alcohol intake were risk factors after recognition of pregnancy^[100].

Characteristics associated with alcohol-related admissions (based on ICD-10 codes) in pregnancy have been studied in Australia: Residence in a remote/very remote area, being Australian-born, having had a previous pregnancy, smoking in the current pregnancy, and presenting late to antenatal care^[101].

These findings would suggest that while many smokers and single women may not have a problem with alcohol, health professionals should perhaps be more aware of potential alcohol problems among these groups and actively ask them about alcohol consumption. To the extent that nulliparous women engage in binge drinking before recognition of pregnancy more often than multiparous women health authorities should focus their information on binge drinking to young women and women planning their first pregnancy.

ATTITUDES AND COMPLIANCE WITH OFFICIAL RECOMMENDATIONS

While it is clear that many health professionals do not seem to recommend abstinence to pregnant women, few studies have assessed what pregnant women actually believe or do, and whether their attitudes and drinking habits are influenced by official recommendations and advice from health professionals.

In a Danish study, 76% of the women considered some alcohol intake during pregnancy to be acceptable, mostly on a weekly level^[102]. Binge drinking, however, was considered to be harmful by 85%^[102]. These attitudes were not associated with knowledge about the official recommendation or with discussions between the woman and her general practitioner or midwife about alcohol during pregnancy^[102]. These results seem to be in line with data from Australia, showing that 72% of pregnant women did not comply with the recent 2009 recommendation of alcohol abstinence during pregnancy^[103].

A few studies have evaluated the potential change in alcohol consumption in relation to changes in guidelines, allowing some alcohol intake in pregnancy: Both in Australia^[104] and in Denmark^[97] no significant or clinically relevant changes in drinking habits were found among pregnant women after relaxation of the

guidelines for sensible drinking during pregnancy.

Most Danish women had received information on alcohol from the mass media or relatives, but most women believed that information about alcohol during pregnancy could best be communicated to them by health personnel^[102]. Only 21% were aware of the official recommendation from the Danish Health and Medicines Authority^[102]. One third had discussed alcohol with their general practitioner or midwife, but these women had mostly been advised that some alcohol intake was acceptable^[102].

THE ROLE OF RANDOM ERROR AND BIAS

It is evident that an average daily intake of alcohol during pregnancy is potentially harmful and should be avoided. However, it is less clear if average weekly intake of alcohol may have adverse effects on foetal development and later child development, since the vast majority of studies show no association. If indeed low, average weekly amounts of alcohol during pregnancy are harmful, the effects are likely to be small. When planning and carrying out studies looking for potentially small differences, the methodological challenges are inherently greater, and assessment of the influence of random error and systematic bias becomes paramount, and this assessment may lead different researchers to different views.

The results of any epidemiological study can potentially be due to random error or bias. Considering the increasing number of studies on the association between prenatal alcohol consumption and adverse pregnancy outcomes, the role of chance becomes an ever more important factor to consider when assessing the evidence. In the case of multiple statistical tests, one or more significant findings - positive or negative - may be expected because of chance alone, even in the absence of a true effect. For example, multiple tests may be conducted and reported in a single paper^[105], or in a meta-analysis, for example the cited review on child neuropsychological development involving numerous studies^[60], where a few significant findings would be expected.

Many of the studies, particularly those with long-term follow-up of children, are hampered by potential selection bias because of low participation rates, or missing information on key variables including key confounders; and because participants and non-participants in some studies differed substantially with respect to a large number of important potential confounders^[106]. One way of dealing with this problem is multiple imputation, which has been used in recent studies^[13].

Publication bias is a potential problem, and if so studies showing no association between alcohol intake and adverse outcomes are most likely to remain unpublished.

Information bias is a possibility in all studies of alcohol during pregnancy^[107]. Generally, it is usually assumed that pregnant women probably tend to underestimate their alcohol intake, whereas overestimation - while not impossible - is unlikely. In prospective cohort studies, non-differential misclassification would be expected, because the outcome is unknown at the time of reporting alcohol consumption. Hence, with two exposure categories, as seen in some studies, results will most likely be biased towards the null, *i.e.*, no effect. Even so, with several exposure categories, non-differential misclassification due to underreporting could be expected to lead to bias away from the null value^[107].

Confounding from important confounders was not accounted for, especially in many studies from the 1980s and early 1990s. Residual confounding is therefore likely to be a problem in many studies, and may explain both findings of adverse as well as beneficial effects.

As suggested by the Newcastle-Ottawa-Assessment-Scores in the recent meta-analysis on child neuropsychological development^[60], few studies achieve very high scores, suggesting ample room for methodological improvement in future studies.

DISCUSSION

Is it possible to reach a common consensus on everyday praxis?

The main arguments for abstinence from alcohol during pregnancy is that no safe level of drinking has been established, and that alcohol induced adverse effects cannot occur in the absence of alcohol intake. While the latter argument is indisputable, the former may be challenged. As suggested above, there is no clear, systematic evidence that intake of a few alcohol containing drinks a week will harm the foetus to any measurable degree.

It is particularly interesting that medical ethics have moved in the direction of increased autonomy and informed choice for patients. The British Medical Association advises that "Doctors should respond honestly to direct questions from patients and, as far as possible, answer questions as fully as patients wish"^[108]. It has been suggested that where the available evidence does not suggest a clear and unambiguous answer to the question "how much is safe to drink during pregnancy?", an honest response would be to communicate this uncertainty to the pregnant woman^[109].

While health authorities generally favour informed choice in many circumstances, based on impartial and neutral information, this principle does not seem to apply when it comes to alcohol in pregnancy. If it did, health personnel should convey to pregnant women the potential harmful but also the potential beneficial effects and the potential uncertainty related to individual vulnerability at low intake levels. No health authorities advocate this, probably based on the assumption that the risk of harming an otherwise healthy foetus (non-

maleficence) should be prioritized over the risk of failing to do good (beneficence)^[109]. For example, in an editorial from 2011, a representative of The Danish Health and Medicines Authority wrote that “it seems that alcohol, especially in the first 3 mo of pregnancy, may increase the risk of miscarriage, low birth weight, preterm birth and delayed development in the uterus - even at low intake levels”^[110], referring to a study on the risk of preterm delivery^[14]. This study showed a significantly increased risk of preterm delivery only for nulliparous women drinking ≥ 7 drinks/wk (OR = 2.91, 95%CI: 1.29-6.55), but a significantly reduced risk for all women drinking 2-3½ drinks/wk (OR = 0.80, 95%CI: 0.68-0.96)^[14].

At the same time it is evident from the few relevant studies that many health professionals do not believe that pregnant women must totally abstain from alcohol^[80-83]. Also, pregnant women in Australia and Denmark did not seem to change their drinking habits, even when less restrictive recommendations were issued^[97,104]. Hence, it seems that the mere existence of an official guideline or recommendation concerning alcohol in pregnancy has not been enough to standardize the information provided to pregnant women and to modify their behaviour in relation to alcohol.

In some cases, guidelines from health authorities are written by civil servants and epidemiologists with no or very limited clinical experience. In Denmark, the literature review and guideline from 1999 allowing a small, weekly intake, was written mainly by clinicians^[75]. The 2007 recommendation of abstinence and the arguments supporting it was written solely by representatives of The Danish Health and Medicines Authority^[76] and two epidemiologists^[111].

Perhaps this is the real issue: Guidelines issued by many health authorities do not take into account the everyday clinical communication, where pregnant women turn up admitting to some alcohol intake, often one drink per week or even less. Health personnel have to advise pregnant women in these situations, and telling the pregnant woman that a single drink may have harmed the foetus is not in line with current evidence. But if one drink is unlikely to harm the foetus, where is the limit? This question is asked every day, and if health authorities do not supply health personnel with an answer, each clinician will have to come up with a responsible answer in line with current evidence.

The Danish Health and Medicines Authority write that “General practitioners and midwives will meet pregnant women, who have a bad conscience, because they have been drinking alcohol, before recognition of pregnancy. These women should be met with a risk assessment based on the existing evidence that intake of one drink a day is associated with a small risk for the child”^[76]. It is left to the health personnel to decide if the focus of the information should be “there is a (small) risk” or “the risk is negligible, so do not worry”.

Most likely the discrepancy between guidelines and recommendations from health authorities and the information practice of health personnel will continue to exist. Mainly because guidelines of total abstinence are not clearly evidence based and not in line with current focus on autonomy and informed choice for patients, and because guidelines may be written by non-clinicians, who do not consider and have no experience with the everyday communication between health personnel and pregnant women.

There is little evidence to support a guideline or recommendation of total abstinence, and considering the vast number of studies already published on the topic, it is perhaps surprising that so few studies suggest a risk at low intake levels. Guidelines recommending abstinence may seem an obvious choice because the message is simple. However, simplistic messages that are not clearly evidence-based do not necessarily answer the specific and detailed questions of pregnant women. Health personnel are faced with an increasing amount of information that they are expected to pass on to pregnant women, including messages about lifestyle, and the information must be given within the context of the individual woman. In the absence of clear evidence that abstinence from alcohol is the only right choice, many clinicians will probably continue to focus on other important aspects of pregnancy rather than insisting that a drink a week or less is potentially harmful.

REFERENCES

- 1 **Aristotle**. Problemata III, 4. Cambridge, Massachusetts: Harvard University Press, 1961
- 2 **Aristotle**. Historia animalium IX, 588a6. Cambridge, Massachusetts: Harvard University Press, 1991
- 3 **Warner RH**, Rosett HL. The effects of drinking on offspring: an historical survey of the American and British literature. *J Stud Alcohol* 1975; **36**: 1395-1420 [DOI: 10.15288/jsa.1975.36.1395]
- 4 **Baumont T**. Remarks made in opposition to the views of Dr. Clutterbuck on abstinence from spirituous liquors. *Lancet* 1842; **2**: 340-343 [DOI: 10.1016/S0140-6736(02)85270-9]
- 5 **J. E.** Reports on idiocy. *Am J Med Sci* 1849; **17**: 421-441
- 6 **Sullivan WC**. A note on the influence of maternal inebriety on the offspring. *J Ment Sci* 1899; **45**: 489-503 [DOI: 10.1192/bjp.45.190.489]
- 7 **Fuchs F**, Fuchs AR, Poblete VF, Risk A. Effect of alcohol on threatened premature labor. *Am J Obstet Gynecol* 1967; **99**: 627-637 [PMID: 6051158]
- 8 **Graff G**. Failure to prevent premature labor with ethanol. *Am J Obstet Gynecol* 1971; **110**: 878-880 [PMID: 5562007]
- 9 **Castrén O**, Gummerus M, Saarikoski S. Treatment of imminent premature labour. *Acta Obstet Gynecol Scand* 1975; **54**: 95-100 [PMID: 1094787 DOI: 10.3109/00016347509156739]
- 10 **Lemoine P**, Harousseau H, Borteyru J P, Menuet J-C. Les enfants de parents alcooliques: Anomalies observées a propos de 127 cas. *Quest méd* 1968; **21**: 476-482
- 11 **Jones KL**, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 1973; **302**: 999-1001 [PMID: 4127281 DOI: 10.1016/S0140-6736(73)91092-1]
- 12 **Kesmodel U**. Self-reported intake of alcohol: methods and approaches. In: Preedy VR, Watson RR (eds). Comprehensive handbook of alcohol related pathology. London: Elsevier, 2004: 1367-1382 [DOI: 10.1016/B978-012564370-2/50104-5]

- 13 **Kesmodel US**, Bertrand J, Støvring H, Skarpness B, Denny CH, Mortensen EL. The effect of different alcohol drinking patterns in early to mid pregnancy on the child's intelligence, attention, and executive function. *BJOG* 2012; **119**: 1180-1190 [PMID: 22712700 DOI: 10.1111/j.1471-0528.2012.03393.x]
- 14 **Albertsen K**, Andersen AM, Olsen J, Grønbaek M. Alcohol consumption during pregnancy and the risk of preterm delivery. *Am J Epidemiol* 2004; **159**: 155-161 [PMID: 14718217 DOI: 10.1093/aje/kwh034]
- 15 **Bertrand J**, Floyd RL, Weber MK, O'Connor M, Riley EP, Johnson KA, Cohen DE, National Task Force on FAS/FAE. Fetal alcohol syndrome: guideline for referral and diagnosis; Atlanta, GA, United States: Centers for Disease Control and Prevention, 2004
- 16 **Hoyme HE**, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, Buckley DG, Miller JH, Aragon AS, Khaole N, Viljoen DL, Jones KL, Robinson LK. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics* 2005; **115**: 39-47 [PMID: 15629980]
- 17 American Academy of Pediatrics Committee on Substance Abuse and Committee on Children with Disabilities: Fetal alcohol syndrome and fetal alcohol effects. *Pediatrics* 1993; **91**: 1004-1006 [PMID: 8507280]
- 18 **Church MW**, Eldis F, Blakley BW, Bawle EV. Hearing, language, speech, vestibular, and dentofacial disorders in fetal alcohol syndrome. *Alcohol Clin Exp Res* 1997; **21**: 227-237 [PMID: 9113257 DOI: 10.1111/j.1530-0277.1997.tb03796.x]
- 19 **Spohr HL**, Willms J, Steinhausen HC. Prenatal alcohol exposure and long-term developmental consequences. *Lancet* 1993; **341**: 907-910 [PMID: 7681518 DOI: 10.1016/0140-6736(93)91207-3]
- 20 **Centers for Disease Control and Prevention**. Fetal Alcohol Spectrum Disorders (FASDs). [accessed 2015 Nov 11]. Available from: URL: <http://www.cdc.gov/NCBDDD/fasd/facts.html>
- 21 **Patra J**, Bakker R, Irving H, Jaddoe VW, Malini S, Rehm J. Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA)-a systematic review and meta-analyses. *BJOG* 2011; **118**: 1411-1421 [PMID: 21729235 DOI: 10.1111/j.1471-0528.2011.03050.x]
- 22 **Kesmodel U**, Olsen SF, Secher NJ. Does alcohol increase the risk of preterm delivery? *Epidemiology* 2000; **11**: 512-518 [PMID: 10955402 DOI: 10.1097/00001648-200009000-00005]
- 23 **Weinberg CR**, Wilcox AJ. Reproductive Epidemiology. In Rothman KJ, Greenland Sed (eds): Modern Epidemiology. Lippincott-Raven, 1998: 585-608
- 24 **Kesmodel U**, Wisborg K, Olsen SF, Henriksen TB, Secher NJ. Moderate alcohol intake in pregnancy and the risk of spontaneous abortion. *Alcohol Alcohol* 2002; **37**: 87-92 [PMID: 11825863 DOI: 10.1093/alcalc/37.1.87]
- 25 **Windham GC**, Von Behren J, Fenster L, Schaefer C, Swan SH. Moderate maternal alcohol consumption and risk of spontaneous abortion. *Epidemiology* 1997; **8**: 509-514 [PMID: 9270952 DOI: 10.1097/00001648-199709000-00007]
- 26 **Andersen AM**, Andersen PK, Olsen J, Grønbaek M, Strandberg-Larsen K. Moderate alcohol intake during pregnancy and risk of fetal death. *Int J Epidemiol* 2012; **41**: 405-413 [PMID: 22253313 DOI: 10.1093/ije/dyr189]
- 27 **Sokol RJ**. Alcohol and spontaneous abortion. *Lancet* 1980; **2**: 1079 [PMID: 6107699 DOI: 10.1016/S0140-6736(80)92296-5]
- 28 **Sokol RJ**, Miller SI, Reed G. Alcohol abuse during pregnancy: an epidemiologic study. *Alcohol Clin Exp Res* 1980; **4**: 135-145 [PMID: 6990816 DOI: 10.1111/j.1530-0277.1980.tb05628.x]
- 29 **Cavallo F**, Russo R, Zotti C, Camerlengo A, Ruggerini AM. Moderate alcohol consumption and spontaneous abortion. *Alcohol Alcohol* 1995; **30**: 195-201 [PMID: 7662038]
- 30 **Dlugosz L**, Belanger K, Hellenbrand K, Holford TR, Leaderer B, Bracken MB. Maternal caffeine consumption and spontaneous abortion: a prospective cohort study. *Epidemiology* 1996; **7**: 250-255 [PMID: 8728437 DOI: 10.1097/00001648-199605000-00006]
- 31 **Parazzini F**, Boccione L, La Vecchia C, Negri E, Fedele L. Maternal and paternal moderate daily alcohol consumption and unexplained miscarriages. *Br J Obstet Gynaecol* 1990; **97**: 618-622 [PMID: 2390506 DOI: 10.1111/j.1471-0528.1990.tb02550.x]
- 32 **Parazzini F**, Tozzi L, Chatenoud L, Restelli S, Luchini L, La Vecchia C. Alcohol and risk of spontaneous abortion. *Hum Reprod* 1994; **9**: 1950-1953 [PMID: 7844232]
- 33 **Zhang H**, Bracken MB. Tree-based, two-stage risk factor analysis for spontaneous abortion. *Am J Epidemiol* 1996; **144**: 989-996 [PMID: 8916510 DOI: 10.1093/oxfordjournals.aje.a008869]
- 34 **McDonald AD**, Armstrong BG, Sloan M. Cigarette, alcohol, and coffee consumption and prematurity. *Am J Public Health* 1992; **82**: 87-90 [PMID: 1536341 DOI: 10.2105/AJPH.82.1.87]
- 35 **Harlap S**, Shiono PH. Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. *Lancet* 1980; **2**: 173-176 [PMID: 6105340 DOI: 10.1016/S0140-6736(80)90061-6]
- 36 **Windham GC**, Fenster L, Swan SH. Moderate maternal and paternal alcohol consumption and the risk of spontaneous abortion. *Epidemiology* 1992; **3**: 364-370 [PMID: 1637900 DOI: 10.1097/00001648-199207000-00012]
- 37 **Strandberg-Larsen K**, Nielsen NR, Grønbaek M, Andersen PK, Olsen J, Andersen AM. Binge drinking in pregnancy and risk of fetal death. *Obstet Gynecol* 2008; **111**: 602-609 [PMID: 18310362 DOI: 10.1097/AOG.0b013e3181661431]
- 38 **Henderson J**, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. *BJOG* 2007; **114**: 243-252 [PMID: 17233797 DOI: 10.1111/j.1471-0528.2006.01163.x]
- 39 **Kesmodel U**, Wisborg K, Olsen SF, Henriksen TB, Secher NJ. Moderate alcohol intake during pregnancy and the risk of stillbirth and death in the first year of life. *Am J Epidemiol* 2002; **155**: 305-312 [PMID: 11836194 DOI: 10.1093/aje/155.4.305]
- 40 **Mills JL**, Graubard BI. Is moderate drinking during pregnancy associated with an increased risk for malformations? *Pediatrics* 1987; **80**: 309-314 [PMID: 3627880]
- 41 **Rostand A**, Kaminski M, Lelong N, Dehaene P, Delestret I, Klein-Bertrand C, Querleu D, Crepin G. Alcohol use in pregnancy, craniofacial features, and fetal growth. *J Epidemiol Community Health* 1990; **44**: 302-306 [PMID: 2277252 DOI: 10.1136/jech.44.4.302]
- 42 **McDonald AD**, Armstrong BG, Sloan M. Cigarette, alcohol, and coffee consumption and congenital defects. *Am J Public Health* 1992; **82**: 91-93 [PMID: 1536342 DOI: 10.2105/AJPH.82.1.91]
- 43 **Damgaard IN**, Jensen TK, Petersen JH, Skakkebaek NE, Toppa J, Main KM. Cryptorchidism and maternal alcohol consumption during pregnancy. *Environ Health Perspect* 2007; **115**: 272-277 [PMID: 17384777 DOI: 10.1289/ehp.9608]
- 44 **Ernhart CB**, Sokol RJ, Ager JW, Morrow-Tlucak M, Martier S. Alcohol-related birth defects: assessing the risk. *Ann N Y Acad Sci* 1989; **562**: 159-172 [PMID: 2742273 DOI: 10.1111/j.1749-6632.1989.tb01014.x]
- 45 **Mukherjee RA**, Hollins S, Turk J. Fetal alcohol spectrum disorder: an overview. *J R Soc Med* 2006; **99**: 298-302 [PMID: 16738372 DOI: 10.1258/jrsm.99.6.298]
- 46 **Mattson SN**, Riley EP, Gramling L, Delis DC, Jones KL. Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. *J Pediatr* 1997; **131**: 718-721 [PMID: 9403652 DOI: 10.1016/S0022-3476(97)70099-4]
- 47 **Streissguth AP**, Barr HM, Sampson PD, Darby BL, Martin DC. IQ at age 4 in relation to maternal alcohol use and smoking during pregnancy. *Dev Psychol* 1989; **25**: 3-11 [DOI: 10.1037/0012-1649.25.1.3]
- 48 **Streissguth AP**, Barr HM, Sampson PD. Moderate prenatal alcohol exposure: effects on child IQ and learning problems at age 7 1/2 years. *Alcohol Clin Exp Res* 1990; **14**: 662-669 [PMID: 2264594 DOI: 10.1111/j.1530-0277.1990.tb01224.x]
- 49 **Connor PD**, Sampson PD, Bookstein FL, Barr HM, Streissguth AP. Direct and indirect effects of prenatal alcohol damage on executive function. *Dev Neuropsychol* 2000; **18**: 331-354 [PMID: 11385829 DOI: 10.1207/S1532694204Connor]

- 50 **Noland JS**, Singer LT, Arendt RE, Minnes S, Short EJ, Bearer CF. Executive functioning in preschool-age children prenatally exposed to alcohol, cocaine, and marijuana. *Alcohol Clin Exp Res* 2003; **27**: 647-656 [PMID: 12711927 DOI: 10.1111/j.1530-0277.2003.tb04401.x]
- 51 **Streissguth AP**, Barr HM, Sampson PD, Parrish-Johnson JC, Kirchner GL, Martin DC. Attention, distraction and reaction time at age 7 years and prenatal alcohol exposure. *Neurobehav Toxicol Teratol* 1986; **8**: 717-725 [PMID: 3808187]
- 52 **Streissguth AP**, Sampson PD, Olson HC, Bookstein FL, Barr HM, Scott M, Feldman J, Mirsky AF. Maternal drinking during pregnancy: attention and short-term memory in 14-year-old offspring--a longitudinal prospective study. *Alcohol Clin Exp Res* 1994; **18**: 202-218 [PMID: 8198221 DOI: 10.1111/j.1530-0277.1994.tb00904.x]
- 53 **Coles CD**, Platzman KA, Lynch ME, Freides D. Auditory and visual sustained attention in adolescents prenatally exposed to alcohol. *Alcohol Clin Exp Res* 2002; **26**: 263-271 [PMID: 11964567 DOI: 10.1111/j.1530-0277.2002.tb02533.x]
- 54 **O'Connor MJ**, Paley B. Psychiatric conditions associated with prenatal alcohol exposure. *Dev Disabil Res Rev* 2009; **15**: 225-234 [PMID: 19731386 DOI: 10.1002/ddrr.74]
- 55 **Richardson GA**, Ryan C, Willford J, Day NL, Goldschmidt L. Prenatal alcohol and marijuana exposure: effects on neuropsychological outcomes at 10 years. *Neurotoxicol Teratol* 2002; **24**: 309-320 [PMID: 12009486 DOI: 10.1016/S0892-0362(02)00193-9]
- 56 **Burden MJ**, Jacobson SW, Jacobson JL. Relation of prenatal alcohol exposure to cognitive processing speed and efficiency in childhood. *Alcohol Clin Exp Res* 2005; **29**: 1473-1483 [PMID: 16131856 DOI: 10.1097/01.alc.0000175036.34076.a0]
- 57 **Shaywitz SE**, Cohen DJ, Shaywitz BA. Behavior and learning difficulties in children of normal intelligence born to alcoholic mothers. *J Pediatr* 1980; **96**: 978-982 [PMID: 7373484 DOI: 10.1016/S0022-3476(80)80621-4]
- 58 **Nordberg L**, Rydelius PA, Zetterström R. Children of alcoholic parents: health, growth, mental development and psychopathology until school age. Results from a prospective longitudinal study of children from the general population. *Acta Paediatr Suppl* 1993; **387**: 1-24 [PMID: 8461621 DOI: 10.1111/j.1651-2227.1993.tb12824.x]
- 59 **Bay B**, Kesmodel US. Prenatal alcohol exposure - a systematic review of the effects on child motor function. *Acta Obstet Gynecol Scand* 2011; **90**: 210-226 [PMID: 21306306 DOI: 10.1111/j.1600-0412.2010.01039.x]
- 60 **Flak AL**, Su S, Bertrand J, Denny CH, Kesmodel US, Cogswell ME. The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. *Alcohol Clin Exp Res* 2014; **38**: 214-226 [PMID: 23905882 DOI: 10.1111/acer.12214]
- 61 **Lewis SJ**, Zuccolo L, Davey Smith G, Macleod J, Rodriguez S, Draper ES, Barrow M, Alati R, Sayal K, Ring S, Golding J, Gray R. Fetal alcohol exposure and IQ at age 8: evidence from a population-based birth-cohort study. *PLoS One* 2012; **7**: e49407 [PMID: 23166662 DOI: 10.1371/journal.pone.0049407]
- 62 **Skogerboe Å**, Kesmodel US, Denny CH, Kjaersgaard MI, Wimberley T, Landrø NI, Mortensen EL. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on behaviour in 5-year-old children: a prospective cohort study on 1628 children. *BJOG* 2013; **120**: 1042-1050 [PMID: 23837773 DOI: 10.1111/1471-0528.12208]
- 63 **O'Callaghan FV**, O'Callaghan M, Najman JM, Williams GM, Bor W. Maternal alcohol consumption during pregnancy and physical outcomes up to 5 years of age: a longitudinal study. *Early Hum Dev* 2003; **71**: 137-148 [PMID: 12663151 DOI: 10.1016/S0378-3782(03)00003-3]
- 64 **Olsen J**, Pereira Ada C, Olsen SF. Does maternal tobacco smoking modify the effect of alcohol on fetal growth? *Am J Public Health* 1991; **81**: 69-73 [PMID: 1983919 DOI: 10.2105/AJPH.81.1.69]
- 65 **Passaro KT**, Little RE, Savitz DA, Noss J. The effect of maternal drinking before conception and in early pregnancy on infant birthweight. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Epidemiology* 1996; **7**: 377-383 [PMID: 8793363 DOI: 10.1097/00001648-199607000-00007]
- 66 **Tolo KA**, Little RE. Occasional binges by moderate drinkers: implications for birth outcomes. *Epidemiology* 1993; **4**: 415-420 [PMID: 8399689]
- 67 **McCarthy FP**, O'Keeffe LM, Khashan AS, North RA, Poston L, McCowan LM, Baker PN, Dekker GA, Roberts CT, Walker JJ, Kenny LC. Association between maternal alcohol consumption in early pregnancy and pregnancy outcomes. *Obstet Gynecol* 2013; **122**: 830-837 [PMID: 24084541 DOI: 10.1097/AOG.0b013e3182a6b226]
- 68 **Henderson J**, Kesmodel U, Gray R. Systematic review of the fetal effects of prenatal binge-drinking. *J Epidemiol Community Health* 2007; **61**: 1069-1073 [PMID: 18000129 DOI: 10.1136/jech.2006.054213]
- 69 **Olsen J**, Tuntiseranee P. Is moderate alcohol intake in pregnancy associated with the craniofacial features related to the fetal alcohol syndrome? *Scand J Soc Med* 1995; **23**: 156-161 [PMID: 8602484 DOI: 10.1177/140349489502300304]
- 70 **Strandberg-Larsen K**, Skov-Ettrup LS, Grønbaek M, Andersen AM, Olsen J, Tolstrup J. Maternal alcohol drinking pattern during pregnancy and the risk for an offspring with an isolated congenital heart defect and in particular a ventricular septal defect or an atrial septal defect. *Birth Defects Res A Clin Mol Teratol* 2011; **91**: 616-622 [PMID: 21591246 DOI: 10.1002/bdra.20818]
- 71 **Danish Health and Medicines Authority**. [Pregnancy & alcohol] Graviditet & Alkohol (Leaflet). Copenhagen, Egmont Fonden and Sundhedsstyrelsen, 1997
- 72 **Joint statement**. Prevention of fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE) in Canada; Ottawa, Health Canada, 1996
- 73 **National Health and Medical Research Council**. Is there a safe level of daily consumption of alcohol for men and women; Canberra: Commonwealth of Australia, 1992
- 74 **National Health and Medical Research Council**. Australian alcohol guidelines: health risks and benefits; Canberra: Commonwealth of Australia, 2001
- 75 **Danish Health and Medicines Authority**. [Pregnancy and alcohol] Graviditet og alkohol. [Prevention and health promotion] Forebyggelse og sundhedsfremme (Report). Copenhagen, Danish National Board of Health, 1999
- 76 **Danish National Board of Health**. Alcohol and pregnancy, 2007. [accessed 2015 Nov 11]. Available from: URL: http://www.sst.dk/publ/Publ2007/CFF/Alkohol_graviditet/Alk_grav.pdf
- 77 **National Health and Medical Research Council**. Australian guidelines to reduce health risks from drinking alcohol; Canberra: Commonwealth of Australia, 2009
- 78 **RCOG**. Alcohol consumption and the outcome of pregnancy; RCOG Statement no. 5, 2013. [accessed 2015 Nov 11]. Available from: URL: http://www.alcoholpolicy.net/files/RCOG_Alcohol_pregnancy_March_06.pdf
- 79 **National Institute for Health and Clinical Excellence**. Antenatal care - routine care for the healthy pregnant woman, 2008. [accessed 2015 Nov 11]. Available from: URL: <http://www.nice.org.uk/nicemedia/pdf/CG062NICEguideline>
- 80 **Payne J**, Elliott E, D'Antoine H, O'Leary C, Mahony A, Haan E, Bower C. Health professionals' knowledge, practice and opinions about fetal alcohol syndrome and alcohol consumption in pregnancy. *Aust N Z J Public Health* 2005; **29**: 558-564 [PMID: 16366068 DOI: 10.1111/j.1467-842X.2005.tb00251.x]
- 81 **Kesmodel US**, Kesmodel PS, Iversen LL. Lack of consensus between general practitioners and official guidelines on alcohol abstinence during pregnancy. *Dan Med Bull* 2011; **58**: A4327 [PMID: 21975156]
- 82 **Diekmann ST**, Floyd RL, Découflé P, Schulkin J, Ebrahim SH, Sokol RJ. A survey of obstetrician-gynecologists on their patients' alcohol use during pregnancy. *Obstet Gynecol* 2000; **95**: 756-763 [PMID: 10775743 DOI: 10.1016/S0029-7844(99)00616-X]
- 83 **Kesmodel US**, Kesmodel PS. Alcohol in pregnancy: attitudes, knowledge, and information practice among midwives in Denmark 2000 to 2009. *Alcohol Clin Exp Res* 2011; **35**: 2226-2230 [PMID: 21975156]

- 21689120 DOI: 10.1111/j.1530-0277.2011.01572.x]
- 84 **Finer LB**, Zolna MR. Unintended pregnancy in the United States: incidence and disparities, 2006. *Contraception* 2011; **84**: 478-485 [PMID: 22018121 DOI: 10.1016/j.contraception.2011.07.013]
 - 85 **The NHS Information Centre LS**. Statistics on alcohol: England, 2009. Available from: URL: <http://catalogue.ic.nhs.uk/publications/public-health/alcohol/alco-eng-2009/alco-eng-2009-rep.pdf>
 - 86 **Kesmodel U**, Kesmodel PS, Larsen A, Secher NJ. Use of alcohol and illicit drugs among pregnant Danish women, 1998. *Scand J Public Health* 2003; **31**: 5-11 [PMID: 12623518 DOI: 10.1080/14034940210134202]
 - 87 **Alvik A**, Heyerdahl S, Haldorsen T, Lindemann R. Alcohol use before and during pregnancy: a population-based study. *Acta Obstet Gynecol Scand* 2006; **85**: 1292-1298 [PMID: 17091405 DOI: 10.1080/00016340600589958]
 - 88 **Göransson M**, Magnusson A, Bergman H, Rydberg U, Heilig M. Fetus at risk: prevalence of alcohol consumption during pregnancy estimated with a simple screening method in Swedish antenatal clinics. *Addiction* 2003; **98**: 1513-1520 [PMID: 14616177 DOI: 10.1046/j.1360-0443.2003.00498.x]
 - 89 **Lifestyle Statistics HaSCIC**. Statistics on alcohol: England, 2013. Available from: URL: <http://catalogue.ic.nhs.uk/publications/public-health/alcohol/alco-eng-2013/alco-eng-2013-rep.pdf>
 - 90 **Centers for Disease Control and Prevention**. Vital signs: binge drinking prevalence, frequency, and intensity among adults - United States, 2010. *MMWR Morb Mortal Wkly Rep* 2012; **61**: 14-19 [PMID: 22237031]
 - 91 **Lorant V**, Nicaise P, Soto VE, d'Hoore W. Alcohol drinking among college students: college responsibility for personal troubles. *BMC Public Health* 2013; **13**: 615 [PMID: 23805939 DOI: 10.1186/1471-2458-13-615]
 - 92 **Acuda W**, Othieno CJ, Obondo A, Crome IB. The epidemiology of addiction in Sub-Saharan Africa: a synthesis of reports, reviews, and original articles. *Am J Addict* 2011; **20**: 87-99 [PMID: 21314750 DOI: 10.1111/j.1521-0391.2010.00111.x]
 - 93 **Centers for Disease Control and Prevention**. Facts sheets - alcohol use and health, 2013. [accessed 2015 Nov 11]. Available from: URL: <http://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm>
 - 94 **Ebrahim SH**, Luman ET, Floyd RL, Murphy CC, Bennett EM, Boyle CA. Alcohol consumption by pregnant women in the United States during 1988-1995. *Obstet Gynecol* 1998; **92**: 187-192 [PMID: 9699749 DOI: 10.1016/S0029-7844(98)00205-1]
 - 95 **Ebrahim SH**, Diekmann ST, Floyd RL, Decoufle P. Comparison of binge drinking among pregnant and nonpregnant women, United States, 1991-1995. *Am J Obstet Gynecol* 1999; **180**: 1-7 [PMID: 9914568 DOI: 10.1016/S0002-9378(99)70139-0]
 - 96 **Osler M**, Kriebaum M, Christensen U, Holstein B, Nybo Andersen AM. Rapid report on methodology: does loss to follow-up in a cohort study bias associations between early life factors and lifestyle-related health outcomes? *Ann Epidemiol* 2008; **18**: 422-424 [PMID: 18329893 DOI: 10.1016/j.annepidem.2007.12.008]
 - 97 **Andersen AM**, Olsen J, Grønbaek MN. [Did the changed guidelines on alcohol and pregnancy by the National Board of Health and Welfare change alcohol consumption of pregnant women?]. *Ugeskr Laeger* 2001; **163**: 1561-1565 [PMID: 11268810]
 - 98 **Olsen J**, Melbye M, Olsen SF, Sørensen TI, Aaby P, Andersen AM, Taxhøf D, Hansen KD, Juhl M, Schow TB, Sørensen HT, Andresen J, Mortensen EL, Olesen AW, Søndergaard C. The Danish National Birth Cohort--its background, structure and aim. *Scand J Public Health* 2001; **29**: 300-307 [PMID: 11775787 DOI: 10.1177/14034948010290040201]
 - 99 **Anderson P**, Baumberg B. Alcohol in Europe - a public health perspective. A report for the European Commission; London, Institute of Alcohol Studies, 2006
 - 100 **Strandberg-Larsen K**, Rod Nielsen N, Nybo Andersen AM, Olsen J, Grønbaek M. Characteristics of women who binge drink before and after they become aware of their pregnancy. *Eur J Epidemiol* 2008; **23**: 565-572 [PMID: 18553140 DOI: 10.1007/s10654-008-9265-z]
 - 101 **Burns L**, Black E, Powers JR, Loxton D, Elliott E, Shakeshaft A, Dunlop A. Geographic and maternal characteristics associated with alcohol use in pregnancy. *Alcohol Clin Exp Res* 2011; **35**: 1230-1237 [PMID: 21463334 DOI: 10.1111/j.1530-0277.2011.01457.x]
 - 102 **Kesmodel U**, Schiøler Kesmodel P. Drinking during pregnancy: attitudes and knowledge among pregnant Danish women, 1998. *Alcohol Clin Exp Res* 2002; **26**: 1553-1560 [PMID: 12394289 DOI: 10.1111/j.1530-0277.2002.tb02455.x]
 - 103 **Anderson AE**, Hure AJ, Powers JR, Kay-Lambkin FJ, Loxton DJ. Determinants of pregnant women's compliance with alcohol guidelines: a prospective cohort study. *BMC Public Health* 2012; **12**: 777 [PMID: 22971176 DOI: 10.1186/1471-2458-12-777]
 - 104 **Powers JR**, Loxton DJ, Burns LA, Shakeshaft A, Elliott EJ, Dunlop AJ. Assessing pregnant women's compliance with different alcohol guidelines: an 11-year prospective study. *Med J Aust* 2010; **192**: 690-693 [PMID: 20565346]
 - 105 **O'Callaghan FV**, O'Callaghan M, Najman JM, Williams GM, Bor W. Prenatal alcohol exposure and attention, learning and intellectual ability at 14 years: a prospective longitudinal study. *Early Hum Dev* 2007; **83**: 115-123 [PMID: 16842939 DOI: 10.1016/j.earlhumdev.2006.05.011]
 - 106 **Sayal K**, Draper ES, Fraser R, Barrow M, Davey Smith G, Gray R. Light drinking in pregnancy and mid-childhood mental health and learning outcomes. *Arch Dis Child* 2013; **98**: 107-111 [PMID: 23322857 DOI: 10.1136/archdischild-2012-302436]
 - 107 **Verkerk PH**. The impact of alcohol misclassification on the relationship between alcohol and pregnancy outcome. *Int J Epidemiol* 1992; **21** Suppl 1: S33-S37 [PMID: 1399217 DOI: 10.1093/ije/21.Supplement_1.S33]
 - 108 **British Medical Association**. Consent tool kit. [accessed 2015 Nov 11]. Available from: URL: <http://bma.org.uk/practical-support-at-work/ethics/consent-tool-kit>
 - 109 **Gavaghan C**. "You can't handle the truth"; medical paternalism and prenatal alcohol use. *J Med Ethics* 2009; **35**: 300-303 [PMID: 19407034 DOI: 10.1136/jme.2008.028662]
 - 110 **Smith E**. A drink may harm the baby in mother's womb. En lille en kan skade barnet i mors mave (editorial). *Ugeskr Laeger* 2011; **46**: 2939
 - 111 **Strandberg-Larsen K**, Grønbaek M. [Memorandum concerning alcohol and pregnancy] Notat vedrørende alkohol og graviditet, 2006. [accessed 2015 Nov 11]. Available from: URL: http://www.sst.dk/publ/Publ2007/CF/Alkohol_graviditet/Notat_alk_grav.pdf

P- Reviewer: Cosmi E, Rasmussen S, Yokoyama Y
S- Editor: Kong JX **L- Editor:** A **E- Editor:** Jiao XK





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

