






WFSBP* and IAWMH** Guidelines for the treatment of alcohol use disorders in pregnant women

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ABSTRACT

Objectives: These practice guidelines for the treatment of alcohol use disorders during pregnancy were developed by members of the International Task Force of the World Federation of Societies of Biological Psychiatry and the International Association for Women's Mental Health.

Methods: We performed a systematic review of all available publications and extracted data from national and international guidelines. The Task Force evaluated the data with respect to the strength of evidence for the efficacy and safety of each medication.

Results and Discussion: There is no safe level of alcohol use during pregnancy. Abstinence is recommended. Ideally, women should stop alcohol use when pregnancy is planned and, in any case, as soon as pregnancy is known. Detecting patterns of alcohol maternal drinking should be systematically conducted at first antenatal visit and throughout pregnancy. Brief interventions are recommended in the case of low or moderate risk of alcohol use. Low doses of benzodiazepines, for the shortest duration, may be used to prevent alcohol withdrawal symptoms when high and chronic alcohol intake is stopped and hospitalisation is recommended. Due to the low level of evidence and/or to low benefit/risk ratio, pharmacological treatment for maintenance of abstinence should not be used during pregnancy. At birth, foetal alcohol spectrum disorders must be searched for, and alcohol metabolites should be measured in meconium of neonates in any doubt of foetal alcohol exposure.

ARTICLE HISTORY

Received 10 July 2018
Accepted 13 July 2018

KEYWORDS



Alcohol; AUD; FASD; pregnancy; women; brief interventions; pharmacological treatment

1. Introduction

Prenatal alcohol exposure is an ongoing major concern and the major cause of avoidable neurodevelopmental disorders. Improvement of our knowledge of alcohol use during pregnancy and its potential consequences for the future child as well as of withdrawal options in

pregnant women who use alcohol is crucial. In the case of alcohol use during pregnancy, we need to promote specific mother/child medical care and foetal alcohol syndrome (FAS) prevention and/or diagnosis.


A recent review of public health interventions (multimedia and educational interventions) aimed at

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 Supplemental data for this article can be accessed [here](#)

This article was originally published with errors, which have now been corrected in the online version. Please see Correction (<http://dx.doi.org/10.1080/15622975.2019.1589235>).

increasing awareness and reducing alcohol consumption in pregnant women concluded that there is poor evidence of effectiveness; improvement in knowledge was reported in six out of seven studies, but the reduction in alcohol use reported in four studies was not significant (Crawford-Williams et al. 2015).

These guidelines are intended for health care providers who manage pregnant women who use alcohol. The aim of these guidelines is to improve the quality of care and to aid in clinical decision-making in this population.

2. Methods

Although these guidelines are based on published evidence, the health care provider is ultimately responsible to select the most appropriate care, based on knowledge of the individual patient.

To achieve these goals, we brought together different views on the appropriate treatment of alcohol use disorders (AUDs) based on existing national and international guidelines, and we conducted an extensive literature search on the use of these medications during pregnancy using the Medline and Embase databases through 2018 supplemented by other sources, including published reviews and national and international guidelines. The guidelines are based on data from publications in peer-reviewed journals. Each recommendation was evaluated by the authors and was discussed with respect to the strength of evidence for its efficacy and especially safety during pregnancy.

2.1. Methods of literature research and data extraction

To update the first set of guidelines, we performed a systematic review (MEDLINE/PubMed database) with the search terms 'alcohol', 'alcoholism', 'pharmacotherapy' and 'pregnancy' to identify all available publications pertaining to alcohol use during pregnancy published in English or with an English abstract until 2018. In addition, we used the following guidelines, consensus papers and sources in the development of these guidelines: American Psychiatric Association, *Practice Guideline for the Treatment of Patients with Substance Use Disorders, Second Edition* (Kleber et al. 2007); World Health Organisation, *Guidelines for the identification and management of substance use and substance use disorders in pregnancy* (WHO 2014); Society of Obstetricians and Gynaecologists of Canada, *Alcohol use and pregnancy consensus clinical guidelines* (Carson et al. 2010);

National Institute for Clinical Excellence (NICE) (2008), *Alcohol use disorders: Diagnosis, assessment and management of harmful drinking and alcohol dependence* (NICE 2011); World Federation of Societies of Biological Psychiatry (WFSBP), *Guidelines for biological treatment of substance use and related disorders, part 1: Alcoholism, first revision* (Soyka et al. 2017); French Alcohol Society and European Federation of Addiction Societies (Rolland et al. 2016); Cochrane Library, *Meta-analyses on the efficacy of different drugs and interventions in alcoholism* (Ntais et al. 2005; Rosner et al. 2010a, 2010b; Sarai et al. 2013; Liu and Wang 2017). Findings from recent meta-analyses (Maisel et al. 2013; Jonas et al. 2014; Donoghue et al. 2015) on the efficacy of anti-craving drugs were also incorporated. These latter guidelines do not specifically address pregnancy but summarise the state of the art of current treatment used for AUDs.

2.2. Rating of recommendations

The recommendations were developed by the authors on the basis of the identified publications and arrived at by consensus with members of the WFSBP Task Force on Addiction Disorders and the WFSBP Task Force on Women's Mental Health as well as the International Association for Women's Mental Health, which is made up of international experts in the field (Bandelow et al. 2008).

3. Epidemiology of alcohol use during pregnancy

Despite the international consensus recommending total abstinence during pregnancy, prenatal alcohol exposure remains a major public health issue.

The prevalence of alcohol use in women increases worldwide over time. The WHO found the rate of current drinking in women was 29% in females, compared with 48% in males (among all 15+ years individuals, from all WHO regions), the prevalence of heavy episodic drinking (defined as drinking at least 60 g or more of pure alcohol on at least one occasion in the past 30 days) was 5.7% in females versus 21.5% in males (among drinkers 15+ years, from all WHO regions). The mean alcohol per capita consumption in 2010 was 8.9 in females versus 21.2 in males (in litres of pure alcohol, among all drinkers 15+ years, from all WHO regions). These epidemiological data are also available per WHO region (Global Status Report on Alcohol and Health, 2014 based on epidemiological studies conducted in 2010) (http://apps.who.int/iris/bitstream/10665/112736/1/9789240692763_eng.pdf?ua=1&ua=1).

During pregnancy, in the USA in 2010, 10–11% of women were using alcohol, which has remained almost unchanged over the last 15 years (Behavioral Risk Factor Surveillance System US 2011–2013) (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6437a3.htm?s_cid=mm6437a3_e (Wendell 2013) or, has slightly decreased (8.7%) (National Survey on Drug Use and Health (2014) (<https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.pdf>); Oh et al. 2017). The prevalence of reported binge drinking (defined as four or more standard drinks on one occasion) was 3.1% in pregnant women versus 18.2% in women of childbearing age in the USA (Behavioral Risk Factor Surveillance System US 2011–2013). A multinational European study showed, on average, 15.8% of women using alcohol during pregnancy; the highest percentages were observed in the UK, Russia and Switzerland ($\geq 21\%$) and the lowest in Norway (4%) (Mårdby et al. 2017). Finally, according to a recent meta-analysis conducted by Popova et al. (2017), the global international prevalence of consuming any amount of alcohol during pregnancy was estimated to be 9.8%, with the highest percentage observed in Europe (25.2%) (Russia, UK, Ireland, Denmark, Belarus were $>36\%$) and the lowest in the WHO Eastern Mediterranean Region countries (i.e., Arabic countries) (0.2%).

There is also an increasing trend towards using multiple substances, either concurrently or alternately, which further increases the risk for the foetus.

4. Risk factors associated with alcohol use during pregnancy

In the literature, the following maternal risk factors were associated with alcohol consumption during pregnancy: young age, unwanted pregnancy, ethnicity (Caucasian-American women drink more alcohol compared to African-American women (Vaughn et al. 1993; Hans 1999)), low levels of prenatal care, living alone, urban living, low socioeconomic status, past history of sexual, physical or emotional abuse, mental health problems, low self-esteem, family conflicts, tobacco use, prepregnancy alcohol use, violent partner, and also having a male partner who uses alcohol, tobacco or illicit drugs (Caetano et al. 2006; Chudley et al. 2007; Ethen et al. 2009; Lamy et al. 2017). According to a review conducted by Skagerström et al. (2011), which assessed data from 14 studies published between 2002 and 2009, the most consistent predictors were prepregnancy alcohol consumption and past history of sexual abuse or exposure to

violence. Unemployment, marital status and education level were less consistent predictive factors.

5. Consequences of prenatal alcohol exposure on neonates and neurodevelopment

Prenatal alcohol exposure is an ongoing major concern as a leading preventable cause of birth defects and developmental disabilities (Chudley et al. 2007; Lamy and Thibaut 2010; Płotka et al. 2014; Lamy et al. 2015; Burd 2016; Cornelius et al. 2016; Del Campo and Jones 2017). The effects of alcohol on foetal brain development may reflect its inherent neurotoxicity, foetal stage of exposure and its pattern of use (frequency, intensity and duration of exposure, as well as concomitant use of other substances such as tobacco or illicit drugs). Heavy episodic drinking and/or binge drinking is associated with the highest risk (Paintner et al. 2012).

In fact, alcohol consumption during pregnancy is associated with a large range of adverse effects including spontaneous abortion, stillbirth, weight and growth deficiencies, birth defects, prematurity and foetal alcohol spectrum disorder (FASD). Children with alcohol-related birth defects (ARBD) might present with heart, kidney, bone or hearing defects. The highest prevalence of ARBD was found in Australia (10.82 per 1,000) (Roozen et al. 2016). FASD, as first described by Lemoine et al. (1968), is characterised by growth deficiencies, craniofacial dysmorphologies and CNS damage (Del Campo and Jones 2017). Indeed, prenatal alcohol exposure can cause intellectual disability, deficits in learning (with memory and executive dysfunctions), attention, language and motor development, poor impulse control and hyperactivity. FAS represents the extreme end of the FASD spectrum. Prenatal alcohol exposure may also result in later mental problems such as depression, anxiety and inappropriate sexual behaviour, increased rate of delinquency or drug and alcohol problems, which might be prevented or attenuated by early diagnosis and management of FASD (Streissguth et al. 1997; Cook et al. 2016). Unfortunately, the diagnosis of FAS or FASD is usually made after birth (sometimes at adult age), when alcohol damage has become irreversible and permanent.

Particularly high-prevalence rates of FAS (55.4 per 1,000) and FASD (113.2 per 1,000) were observed in South Africa; high rates of partial FAS were found in Croatia (43 per 1,000), Italy (36.89 per 1,000) and South Africa (28.3 per 1,000) (Roozen et al. 2016). Lange et al. (2017) reported a worldwide prevalence of FAS of 7.7 per 1,000. Studies using in-person

assessment of school-aged children in several US communities reported a prevalence of FAS of 6–9 out of 1,000 children. Based on community studies using physical examinations, experts estimate that the full range of FASD in the United States and some Western European countries might be as high as 2–5 per 100 school children (May et al. 2009, 2014). Finally, according to a recent meta-analysis conducted by Popova et al. (2017), the worldwide prevalence of FAS among the general population was estimated to be 14.6 per 10,000 people. In line with the prevalence of alcohol use during pregnancy, the prevalence of FAS was the highest in Europe (37.4 per 10,000) (especially in Belarus, Italy, Ireland and Croatia) as well as in South Africa (585.3 per 10,000) and the lowest in the WHO Eastern Mediterranean Region countries (Arabic countries) (0.2–0.9 per 10,000). On the basis of data obtained in seven countries (Australia, Canada, Croatia, France, Italy, South Korea and USA) with prevalence of both alcohol use during pregnancy and FAS available, these authors estimated that one in every 67 mothers who consumed alcohol during pregnancy delivered a child with FAS; in fact a pregnant mother using alcohol will not necessarily give birth to a child with FAS (Popova et al. 2017).

Research evidence is inconclusive about the effects of low levels of alcohol use during pregnancy and its risk for the foetus, although some prospective studies have reported that light drinking during pregnancy (two standard drinks per week (Kelly et al. 2013) to a maximum of six (Robinson et al. 2010)) was not associated with cognitive or behavioural problems in childhood (Kelly et al., 10,534 7-year-old children interviewed; Robinson et al., 2900 pregnancies, self-reports of alcohol use at 18 and 34 weeks of pregnancy, 14-year follow-up for children); for reviews, see Henderson et al. (2007) (focussed on antenatal binge drinking) and DeVido et al. (2015). However, a toxic effect of alcohol is well documented with moderate to heavy levels of exposure; 30–40 g per occasion and as little as or more than 70 g per week have been demonstrated to increase the risk of child behaviour problems (O’Leary and Bower 2012).

Animal models of prenatal ethanol exposure illustrate an alcohol-induced increase in birth defects, including neurological dysfunction; exposure during all gestational periods can have dramatic teratogenic consequences. There are reports of a decrease in spinal and cranial motor neuron production and size, neocortical and hippocampal dysgenesis, increased apoptosis, reduced or delayed neuronal migration and decreased myelination. In addition to its direct toxic

effects on the foetus, alcohol may also act on the hypothalamic–pituitary–adrenal (HPA) axis of both the foetus and the mother, with programming effects on the foetal HPA axis that will contribute to a HPA axis dysregulation during adulthood including hyper-responsiveness to stressors (especially in female offspring), increased HPA axis drive and deficits in HPA axis feedback regulation (Weinberg et al. 2008; for a review, see Thompson et al. (2009)). Thus, prenatal alcohol exposure can be considered an adverse early life event that results in HPA axis abnormalities similar to those seen in depression, which could underlie an increased vulnerability to depression in adulthood (Weinberg et al. 2008).

6. Detection of alcohol use and AUDs during pregnancy (questionnaires and biological markers)

6.1. Questionnaires

Screening aims to identify current or potential alcohol use. Detecting patterns of maternal alcohol drinking is critical to diagnosis, treatment, and prevention of FASD, but is challenging. Information on drinking collected during pregnancy (based on self-reports or semi-structured interviews such as the Addiction Severity Index (McLellan et al. 1992)) is often insufficient or lacking. The reasons for underreporting alcohol use during pregnancy may include among others: fear of forced treatment or legal sanctions in certain US states or in other countries (DeVile and Kopelman 1998), stigmatisation, lack of insurance, lack of specialised treatment facilities for pregnant women, etc. Yet, according to Alvik et al. (2006), self-report remains the best available method to obtain information about moderate alcohol consumption. In fact, there is a very narrow window of detection for alcohol using breath or blood, and other biological measures are not particularly accurate. In addition, self-report screening opens up the door to a discussion of alcohol use (see also Section 8).

Gynaecologists, obstetricians, general practitioners (GPs), midwives and nurses are in an ideal position to screen women for alcohol consumption during pregnancy; indeed, all perinatal caregivers have an important role in counselling women on the importance of avoiding alcohol, using brief interventions (BIs), as well as referring women to specialised treatment units if necessary. Such counselling was recommended for emergency wards, general primary care and gynaecological and obstetric settings by the American Congress of Obstetricians and Gynaecologists (ACOG

Committee Opinion N 422, 2008). In fact, screening for alcohol use, as well as tobacco, illicit drug and psychotropic drug misuse, should be universal in pregnant women whatever their socioeconomic class and ethnicity, at the first prenatal visit, and subsequently throughout pregnancy (American Medical Association, American Congress of Obstetricians and Gynecologists, American Academy of paediatricians; for a review, see Wright et al. 2016). First prenatal visit screening only based on risk factors should be avoided as it may increase stigma and stereotyping (Chasnoff et al. 1990). More widely, screening should be conducted regularly in every woman of childbearing age at medical examinations and especially if a pregnancy is planned (of the 213 million pregnancies that occurred in 2012, 60% were planned (53% in the USA) (Sedgh et al. 2014)). Screening can be conducted by anyone, using validated questionnaires or simply by asking open-ended standardised questions (e.g., the National Institute on Drug Abuse quick screen, which has not yet been validated in pregnant women). The latter questionnaire uses the following questions: 'In the past year, how many times have you drunk more than four alcoholic drinks per day? Used tobacco? Taken illegal drugs or prescription drugs for non-medical reasons?' (Resource guide: screening for drug use in general medical settings. March 2012. Available at: <https://www.drugabuse.gov/publications/resource-guide-screening-druguse-in-general-medical-settings/nida-quick-screen>).

In general, questionnaires are available to detect alcohol use and its associated disorders, but few are specifically designed for use in pregnant women. Unfortunately, none are in widespread use in prenatal care settings despite evidence to suggest that screening in itself can reduce alcohol consumption (Burns et al. 2010).

The AUDIT (Saunders et al. 1993) is a ten-item questionnaire covering alcohol consumption, drinking behaviour and alcohol-related problems during the past 12 months. It takes about 2 min to complete. An overall total score of $\geq 6/40$ is considered positive. Its positive predictive value is limited for alcohol withdrawal syndrome (Lundin et al. 2015).

The AUDIT-C (Bush et al. 1998) is composed of the first three questions of the AUDIT and is easier and quicker to administer. It is a practical screening test for heavy drinking and/or active alcohol abuse or dependence. An overall total score $\geq 3/12$ is positive.

The Fast Alcohol Screening Test (FAST) is a four-item screening tool extracted from the AUDIT. It takes less than 1 min to complete. An overall total score of ≥ 3 is positive (Jones 2011).

The CAGE screening test (Mayfield et al. 1974; Williams 2014) is an acronym of its four questions: feeling need to Cut down; Annoyed by criticism; Guilty about drinking; need for an 'Eye-opener' in the morning. The questions relate to the whole of the patient's life. A total score of $\geq 2/4$ is positive. Initially, it was not developed for use in pregnant women.

The TWEAK (Chan et al. 1993) is a five-item derivative of the CAGE. It is an acronym of the first letter of the key words in the questions: alcohol 'Tolerance', others 'Worry' about drinking, 'Eye-opener' or morning drinking, 'Amnesia' or blackouts and the need to cut 'K' down on drinking. A total score of $\geq 2/7$ is positive.

The SMAST (Selzer et al. 1975) is a shorter version of the MAST (Michigan Alcoholism Screening Test) using 13 (yes/no) questions about the past 12 months.

The T-ACE (Sokol et al. 1989) is a four-item derivative of both Michigan Alcoholism Screening Test and CAGE with a higher sensitivity in pregnant women. It is an acronym of the first letter of the key words in the questions: T, alcohol Tolerance; A, ever Annoyed by someone criticising your drinking; C, the need to Cut down; E, Eye-opener or morning drinking. A total score of $\geq 2/5$ is positive. It takes about 1 min. It was developed for detecting risk drinking in pregnant women. The T-ACER3 is a shorter version with a cut off at 3, with an increased specificity.

The NET (Bottoms et al. 1989) is an acronym of the first letter of the key words in the questions: N, Normal drinker; E, Eye-opener; T, Tolerance. It was developed for use in an obstetric population. It takes about 1 min to complete. An overall score of $>1/4$ is positive.

The SURP-P (Yonkers et al. 2010) is a three-question tool, easy to administer, for all substance use including alcohol, during pregnancy. A cut off score of ≥ 1 is used.

According to Burns et al. (2010), TWEAK, T-ACE and mostly AUDIT-C had the highest sensitivity for identifying prenatal risk drinking. Sensitivity values indicate that about seven to nine of ten risk drinkers would be identified correctly using one of these brief questionnaires. AUDIT-C may also be useful for identifying alcohol dependency or abuse. In contrast, the positive predictive value of T-ACE and TWEAK was low, indicating that for every woman identified correctly with the questionnaire, three women could be identified falsely as risk drinkers.

CAGE and SMAST were poor at identifying risk drinking (Russell et al. 1996).

Finally, Chang et al. (1998) reported that the T-ACE improved the detection of alcohol use during

pregnancy compared to simply asking about alcohol use during prenatal visits. T-ACE and TWEAK inquire about past drinking rather than current pregnancy to avoid denial. Past drinking predicts drinking levels during pregnancy (Harrison and Sidebottom 2009).

The main disadvantage of these tests is their dependence on the cooperation, comprehension, self-reflexion and honesty of the patient who may under-report alcohol use and AUDs during pregnancy. Screening identifies problem drinkers among pregnant women. In addition to screening tests, it is also important to quantify the amount of alcohol used and to remember that the risk of alcohol use in pregnancy starts at very low levels during pregnancy.

The best is to identify and treat AUDs in women before pregnancy so that there is a chance of reducing alcohol use in time before pregnancy. The National Institute for Health and Clinical Excellence (NICE) guidelines recommend detailed screening for alcohol consumption prenatally to identify high-risk or problem drinking (Antenatal care routine care for the healthy pregnant woman. 2008. Available at: <http://www.nice.org.uk/nicemedia/pdf/CG62FullGuidelineCorrectedJune2008.pdf>).

6.2. Biological markers

Specific serum assessments, including aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase (γ GT), mean corpuscular volume (MCV) and especially carbohydrate-deficient transferrin (CDT), appear to be the most efficient laboratory markers for detecting excessive alcohol consumption in pregnant mothers. The window of detection for alcohol using breath or blood is very narrow. Measurements can also be conducted in urine but are not particularly reliable. Direct products of alcohol degradation such as ethyl glucuronide (EtG) and ethyl sulphate as well as fatty acid ethyl esters (FAEEs) are also biomarkers of alcohol use during pregnancy. The latter substances can be measured in the mother's hair or the newborn's meconium. However, women do not like having the hair test. Some data suggest that hair treatments and type of hair can affect the results. Recently, measurements in meconium emerged as reliable, direct biological markers for establishing gestational ethanol exposure during the last trimester (Lamy and Thibaut 2011). Interestingly, Lamy et al. (2017) observed almost no correlation between maternal self-reports of alcohol use during the third trimester and EtG qualitative measurements in meconium samples. In the same way, Lange et al. (2014), in a literature review,

concluded that the prevalence of prenatal exposure was 4.3 times higher according to meconium measurements of FAEEs compared to maternal self-reports. According to Himes et al. (2015), in populations with heavy drinking, where gestational alcohol consumption is not generally socially discouraged, percentages of denying self-reports may be lower. Meconium obtained is post delivery when it is too late to minimise foetal exposure, but in the case of positive measurements of alcohol metabolites at birth, neonates should be carefully followed-up in order to search for FASD. Moreover, according to the FASD Advisory Workgroup recommendations, mothers' interviews must be associated with biological measurements of alcohol consumption to reduce interview biases during pregnancy. In the case of any at-risk alcohol use during pregnancy, meconium measurements of alcohol metabolites should be carried out (Lange et al. 2014; Himes et al. 2015; Lamy et al. 2017).

7. Definition of at-risk pregnant women groups

The term pregnancy risk drinking was previously defined as the consumption of 1 ounce (28 g) or more of alcohol per day (Sokol et al. 1989).

The majority of pregnant women will belong to the low-risk category (no past or current use of tobacco or illicit drugs, low levels of alcohol use in the past, stopped prior to or immediately following knowledge of pregnancy). In these latter cases, no intervention (in case of no risk) or when appropriate (in case of low risk), brief advice/reinforcement are recommended (e.g., 'That is great you do not use tobacco, alcohol or drugs as it has been shown to cause many complications in pregnancy and problems with your baby, as there is no safe amount of alcohol during pregnancy'). Providing written information (flyers) to all girls and women is also important (Yonkers et al. 2012).

Moderate-risk women have used high quantities of alcohol in the past. Those who stopped late during pregnancy or continued low levels of use during pregnancy (two to six standard drinks per week; 20–60 g of pure alcohol per week) are also considered at moderate risk. These women may benefit from BIs and frequent follow-up visits.

Finally, 4–5% of women will belong to the high-risk category (current use of high doses: 30–40 g per occasion and ≥ 70 g of pure alcohol per week (seven standard drinks)). In addition to BIs, these women need

referral to specialised addiction treatment for alcohol withdrawal and frequent follow-up visits.

However, lower levels of alcohol consumption during pregnancy can lead to negative outcomes. No safe level of alcohol consumption during pregnancy has been identified. A study of more than 5,000 pregnant women who consumed alcohol moderately (defined as at least 3.5 standard drinks per week) demonstrated that the group of women who drank more than three standard drinks per week increased significantly their risk of first-trimester spontaneous abortion (Windham et al. 1997).

8. Potential barriers to screening for alcohol use during pregnancy

Identifying women who drink alcohol during pregnancy remains challenging. Gynaecologists, obstetricians, midwives or GPs have to screen all women for any alcohol use during pregnancy.

Their knowledge of how to screen for and to manage alcohol use during pregnancy is essential, direct communication between all caregivers is also crucial. In the case of alcohol exposure during pregnancy, communication between the obstetric team and the paediatrician before and around birth is imperative to identify and treat medical and behavioural problems related to FASD (Wright et al. 2016).

In all cases of tobacco or alcohol withdrawal, partners should be involved regarding information and included in a treatment plan, especially when they are also users and when the woman consents to it.

Yet, there are some barriers about identifying alcohol consumption in pregnancy and its consequences. They include lack of time that care providers have available, concerns about the patients' sensitivity, need for training in the use of questionnaires or for asking questions about alcohol use (e.g., someone saying 'you don't drink alcohol, do you?' is not helpful), lack of adequate referral resources for management of alcohol use once identified; lack of knowledge about the amount of alcohol that is harmful and specific risks associated with its use during pregnancy, especially FASD; lack of access to information brochures for women about alcohol use during pregnancy; and the lack of national and international guidelines about addressing alcohol use in pregnant women (for a review, see Payne et al. 2014). In women who had not stopped alcohol during pregnancy, midwives were worried that they would alienate the patient if they discussed alcohol use (Doi et al. 2014). Anderson et al. (2010) reported that among 800 fellows of the

American College of Obstetricians and Gynaecologists (half of them returned the survey), 82% asked all pregnant women about alcohol use at the initial visit, whereas only 10.6% asked during the initial plus further visits, and 78.5% recommended abstinence. Only half of them used any assessment tool. Barriers to implementing instrument-based screening include patient discomfort, time pressure for health providers (if questionnaires are too long), lack of administrative support, etc. (Bentley et al. 2007).

9. Alcohol withdrawal syndrome (AWS)

In the case of abrupt cessation or fast reduction of chronic alcohol consumption, an AWS may occur. The Prediction of Alcohol Withdrawal Severity Scale (PAWSS) is the first validated questionnaire to identify patients at risk for complicated alcohol withdrawal (seizures and delirium tremens (DT)), allowing for prophylactic treatment. The threshold score is 4 (Maldonado et al. 2015). There are few data on the symptoms and effects of AWS in pregnant women.

The DSM-5 criteria (American Psychiatric Association 2013) for AWS are the presence of two or more of the following symptoms developing within hours to a few days of the intentional or unintentional abrupt cessation or reduction of heavy and prolonged alcohol use: autonomic hyperactivity (sweating, fast pulse), increased hand tremors, insomnia, nausea and/or vomiting, transient hallucinations or perceptual disturbances of the auditory, visual or tactile type, psychomotor agitation, anxiety and generalised seizures. The ICD-10 criteria are similar to those of the DSM-5 (WHO 1992; American Psychiatric Association 2013). Most symptoms of alcohol withdrawal are non-specific. Gait disturbances, paranoid ideas and increased systolic blood pressure are also frequently associated with a severe AWS. In early stages, symptoms are usually limited to autonomic symptoms, tremor, hyperactivity, insomnia, and headache. In minor withdrawal, patients have intact orientation and are fully conscious. Hallucinations (mostly visual) and illusions with disorientation while conscious are symptoms of moderate withdrawal. AWS occurs in approximately 8% of hospitalised AUD inpatients (Perry 2014). Withdrawal symptoms may last for up to 1 week. In addition, more serious symptoms such as severe hallucinations, delirium tremens, alcohol-related psychotic symptoms and generalised tonic-clonic seizures can occur in 15% of severe AUD patients and are associated with an increased mortality risk (Menecier et al. 2008; Chan et al. 2009).

A number of possible candidate genes mediating the risk or the severity of delirium tremens have been suggested, including some genes coding for dopamine receptors or transporters (Van Munster et al. 2007; Dutta et al. 2016). As upregulation of *N*-methyl-D-aspartate (NMDA) receptors as well as reduced γ -amino-butyric acid (GABA-A) receptor inhibition largely explain the clinical symptoms, the therapeutic approach to AWS mainly targets these mechanisms (Jesse et al. 2017). Although, alcohol withdrawal may induce a hypercortisol state (Heinz et al. 1995; Adinoff et al. 1998), there is also a decreased responsiveness of the HPA axis during abstinence, potentially resulting in an impaired capacity to cope with relapse-inducing stressors (Adinoff et al. 1998).

To measure the intensity of alcohol withdrawal symptoms, the most frequently used scale is the Clinical Institute Withdrawal Assessment–Alcohol, revised scale (CIWA-Ar) (Sullivan et al. 1989). This scale is used to determine the severity of the withdrawal symptoms, but does not predict which patients are at risk for withdrawal. It is a ten-item questionnaire, which examines agitation, anxiety, auditory disturbances, orientation and clouding of sensorium, headache, paroxysmal sweats, nausea and vomiting, tactile disturbances, tremor, and visual impairment. It takes about 5 min to complete. Scores <10/67 usually indicate mild withdrawal that may not need medication prophylaxis, scores between 10 and 18 mean moderate-to-severe withdrawal and any score >18/67 indicates a patient at risk for major complications if not treated so that medication is required (Waye et al. 2015; Jesse et al. 2017). This scale might be useful in pregnant women in order to avoid unnecessary benzodiazepine (BZD) use (see also Section 13.2 and Table 3, pharmacological treatments of AUDs; and Section 12.2.1, BZD safety during pregnancy).

10. Behavioral interventions

10.1. Overview of behavioural interventions

A BI is a patient-centered form of counselling that uses brief versions of cognitive behavioural therapies and motivational interviewing or some combination of both (<http://www.Integration.samhsa.gov/clinical-practice/sbirt/brief-interventions>). Its major aim is to help individuals (such as pregnant women), at risk of AUDs, understand how alcohol use puts them at risk and to help them to change their drinking behaviour through time-limited assistance. BIs can also be used to encourage pregnant women with more serious dependence to accept more intensive treatment in

primary care settings or to facilitate referral to specialised treatment programmes and alcohol withdrawal. However, BIs are not intended to treat people with severe alcohol dependence (Substance Abuse and Mental Health Services Administration (SAMHSA); <http://www.Integration.samhsa.gov/clinical-practice/sbirt/brief-interventions>).

BIs can be performed by professionals from different backgrounds. They may vary from counselling sessions with a professional (5 min of brief advice to 15–30 min of brief counselling) (face-to-face or by phone) to self-applied interventions using manuals or computer-based tools. Some programmes were specifically developed for pregnant women. They comprise between one and four brief counselling sessions with a trained professional (e.g., midwife, general practitioner, social worker, etc.) followed by personal feedback. BI general principles include (in addition to feedback on alcohol use and information on the adverse effects of alcohol during pregnancy): expressing empathy, asking open-ended questions followed by summary statements, providing feedback of personal responsibility, using a supportive and non-judgemental style when listening the patient's motivation for using alcohol while exploring other options with the patient, developing trust and rolling with resistance (which means redirecting the conversation to a less-threatening area if necessary), which derive from motivational interview (MI) principles (Miller and Rollnick 1991; Winhusen et al. 2008). In the case of a pregnant women, the principle of MI, which might be part of BIs, is to motivate her to change her behaviour by pointing out discrepancies between her current behaviour and her goals, which are, among others, to give birth to a healthy baby.

10.2 BIs during pregnancy

Schorling (1993) reviewed the existing literature in pregnant women until 1992 and concluded that there were many methodological biases in the published studies comparing BIs and usual care; no studies were randomised, and only two compared a treatment group to a control group (Chang et al. 1999; Handmaker et al. 1999). No difference in alcohol use was observed between control and intervention groups. Chang et al. (2005) reported that both BI and control groups reported reduced alcohol use without significant differences; however, BIs were more effective in reducing alcohol consumption in women with the highest levels of alcohol use, and the effect of BIs were significantly enhanced when partners were involved. A Cochrane

systematic review pooled randomised controlled trials (RCTs) of educational and psychological interventions used to reduce alcohol use during pregnancy versus usual care (Stade et al. 2009). Four randomised controlled North-American studies RCT, including 715 pregnant women (Reynolds et al. 1995; Chang et al. 1999; Handmaker et al. 1999; O'Connor and Whaley 2007a) were analysed. The interventions ranged from a 10-min education session with assessment of alcohol use and provision of a self-help manual to a 1-h MI with reinforcement at each prenatal visit. Controls received routine care including assessment of alcohol use, which may include advice on reducing alcohol intake. Outcomes were measured in different ways and were difficult to compare. The studies provided very limited information on the effects of interventions on the health of women and their babies. For most outcomes there were no significant differences between groups and results relating to abstaining or reducing alcohol consumption were mixed. Results from individual studies suggested that interventions may encourage women to abstain from alcohol in pregnancy. In the O'Connor and Whaley study (2007b), not included in the previous analysis), pregnant women who reported alcohol use were receiving assessment-only or BI (10–15 min of counselling by a trained nutritionist) and were followed until the third trimester of pregnancy. Interestingly, in the BI group, compared to the assessment group, women were five times more likely to report abstinence by the third trimester, newborns had significantly higher birth weight and length and, finally, foetal mortality rate was three times lower. Osterman et al. (2014, RCT) tested the effectiveness of a single session of MI (vs usual care) to decrease alcohol use in 122 pregnant women. MI was not effective in decreasing alcohol use at 30-day post-baseline, and 30-day post-partum follow-ups; however, low levels of alcohol use were reported at baseline. Finally, and interestingly, Joya et al. (2016) measured EtG in hair in 168 pregnant women at antenatal visit. One-third of pregnant women showed hair EtG values corresponding to ethanol drinking, contrasting with negative self-reports. These pregnant women were receiving either one single session of MI (83 cases) versus usual care (85 cases). MI helped in decreasing alcohol consumption assessed by hair EtG measures in the second and third trimesters, but did not increase complete abstinence.

10.3. BIs computer version during pregnancy

Armstrong et al. (2009, RCT) compared two types of BI versus a no-treatment control group in 908 pregnant

women (one focussed on abstinence; and the second one on reducing consumption including a computer-based assessment of alcohol consumption). Controls' neonates had lower birth weights, no differences were observed between the two types of BI. Nilsen et al. (2010) compared standard care in Sweden to the AUDIT-C-based counselling in pregnant women. The latter group was more often satisfied but no differences were observed. Tzilos et al. (2011; RCT) used a computer-delivered BI (15–20 min; tailored content plus education about FASD) versus assessment-only (brochure) in 50 pregnant women considered at-risk alcohol drinkers. Both groups decreased alcohol use at 1-month but without any difference, except for significantly higher birth weights observed in the BI group. In the Ondersma et al. study (2015), 48 pregnant women who screened positive for alcohol risk were randomly assigned to a computer-delivered screening and BI (e-SBI) plus mailings or to a control session on infant nutrition. The e-SBI group showed a non-significant advantage in birth weight and the number of live births, with an increased rate of post-partum abstinence. Harris and Knight (2014) reviewed technology-facilitated screening and BI tools that were evaluated in primary care, paediatric and emergency departments. There were no differences between BI and usual care at 1 month, with a significant reduction in drinking alcohol in both groups. Somehow, babies born to women in the BI group had higher birth weights.

In summary, individual studies suggest that interventions may encourage pregnant women to decrease alcohol use; in several studies, babies born to women in the BI groups showed higher birth weights. Some studies found that people are more likely to report high consumption on computer self-administered questionnaires compared to face-to-face interviews (Yeganeh et al. 2013).

10.4. BIs used in at-risk women in the preconceptional period

To prevent alcohol-exposed pregnancies, it is important to include all women of the childbearing age group who use alcohol in prevention programmes. It seems that risky prepregnancy drinking is a strong predictor of drinking during pregnancy (Ethen et al. 2009). Accordingly, BIs should be performed in women of the childbearing age group in order to prevent many women from drinking alcohol during the first trimester before recognition of pregnancy, this is especially true in low-income groups and heavily drinking women (O'Connor and Whaley 2007b). In general, BIs

and especially MIs appear to have a greater impact on alcohol use in women during the preconceptional period compared to the pregnancy period (Floyd et al. 2007; Ceperich and Ingersoll 2011; Ingersoll et al. 2013; Rendall-Mkosi et al. 2013). Depression and a greater number of binge drinking episodes at baseline were predictors of alcohol reduction (Penberthy et al. 2013; Montag et al. 2015b). Among studies conducted in college students before pregnancy, gender differences pointed to better effects among females especially when online interventions were used (for a review on BI and alcohol use in women, see Gebara et al. 2013). In contrast, Delrahim-Howlett et al. (2011) did not find a significant group effect at 2 months of Web-based alcohol assessment plus computerised BI. Finally, the number of drinks per week and binge episodes were decreased across time for at least 6 months, but without any difference between 20 min online BI and usual care including information (Montag et al. 2015a).

10.5. Methodological issues in BI studies

In the general population, Bertholet et al. (2005) analysed eight out of 17 randomised trials and showed a significant but delayed effect of BIs on alcohol use at 6 or 12 months of follow-up in outpatients attending primary care facilities but not seeking help for AUDs. In contrast, Hetteema et al. (2005) conducted a meta-analysis on 72 clinical trials using MIs; the effect of an MI may peak early and dissipate quickly over time. More recently, Platt et al. (2016), in a systematic review and metaregression, reported that BIs slightly reduced the quantity of alcohol consumed (brief advice appeared slightly more effective than MI whatever the setting); interventions delivered by nurses had the most significant effect in reducing quantity but not frequency of alcohol use.

In fact, assessment per se may have an effect on at-risk drinking. Previous studies have identified a potential active role of assessment alone in reduction in alcohol use over time. This may have contributed to the lack of difference reported in many studies between BI and usual care, including information about alcohol and assessment of alcohol use. Interestingly, Kypri et al. (2007, RCT) confirmed the potential beneficial effect of assessment on hazardous drinking in a general population of 576 students (50% females). Bernstein and Heeren (2010) came to the same conclusion in a systematic review of 16 studies.

11. Summary of the main guidelines concerning AUDs and their management in the general population

Several guidelines have been published concerning AUDs in the general population (NICE in 2011, Alcohol Guidelines Review – Report from the Guidelines Development Group to the UK Chief Medical Officers in 2016; WFSBP guidelines for biological treatment of substance use and related disorders (part 1: alcoholism) (Soyka et al. 2017)). However, few of them were specifically focussed on gender differences or pregnancy. For women, low-risk drinking was defined as no more than three standard drinks on any single day and no more than seven standard drinks per week (National Institute on Alcohol Abuse and Alcoholism); the WHO (2014) recommends, for women, no more than two standard drinks per day (maximum 14 per week including at least 1 day per week without alcohol), no more than four standard drinks on one occasion and no alcohol during pregnancy. It is important to know that standard drinks and recommendations may substantially differ according to countries (see Table 1 below, from Latino-Martel et al. (2011)).

Table 1. Alcohol content of a standard drink and recommendations for alcohol use in different countries.

Country	Pure alcohol content of a standard drink (g)	Recommended upper limits for an adult woman (standard drink)	Institutional source
Australia	10	2 drinks/day (20 g/day)	National Health and Medical Research Council
Austria	8	2 drinks/day (16 g/day)	Ministry of Health
Bulgaria	15	8 g/day	National Center of Public Health Protection
Canada	13.6	2 drinks/day (27.2 g/day) 9 drinks/week (122.4 g/week)	Center for Addiction and Mental Health
Denmark	12	14 drinks/week (168 g/week)	Ministry of Health and Prevention, National Board of Health
France	10	2 drinks/day (20 g/day)	French Institute for Prevention and Health Education
Great Britain	8	2–3 drinks/day (16–24 g/day)	National Health Service
Ireland	10	14 drinks/week (140 g/week)	Health Service Executive
Italy	12	1–2 drinks/day (12–24 g/day) ≥ 65 year: 1 drink/day (12 g/day)	Ministry of Health
Spain	10	11 drinks/week (110 g/week)	Ministry of Health
United States	13.7	1 drink/day (13.7 g/day)	Centers for Disease Control and Prevention; US Department of Health and Human Services

11.1. Treatment of AWS

A number of reviews and evidence-based guidelines have been published concerning the management of AWS (Mayo-Smith 1997; Berner et al. 2004; Lingford-Hughes et al. 2004; Kleber et al. 2007; Bhat and Hadley 2015; Soyka et al. 2017). The main goals of AWS treatment are the immediate relief of symptoms (i.e., agitation and related symptoms) and the prevention of complications. Although alcohol detoxification is usually conducted in outpatients, patients with severe symptoms, extremely high chronic alcohol intake, significant somatic or psychiatric symptoms or delirium tremens should be hospitalised. Risk factors for severe withdrawal syndromes and delirium tremens are concurrent physical illness, high and chronic alcohol intake and a previous history of severe withdrawal symptoms (Soyka et al. 2017).

In general, supplementation of thiamine, to prevent the development of Wernicke-Korsakoff syndrome and repletion of nutrient, fluid and mineral deficiencies are recommended.

Treatment of AWS has traditionally focussed on medications that modulate the GABA receptor system such as BZDs or the NMDA receptors. Results from placebo-controlled studies showed that BZDs reduce withdrawal symptoms (Berglund et al. 2003; Ntais et al. 2005). They are considered worldwide as first-line treatment of AWS and delirium tremens; they reduce anxiety, agitation and symptoms of autonomic hyperactivity (e.g., tremor, palpitations and sweating). They also reduce the incidence and severity of delirium and seizures. The most commonly used BZDs are diazepam, chlordiazepoxide, oxazepam, lorazepam and alprazolam (Level A, Grade 1, according to WFSBP guidelines). Short-acting BZDs, such as lorazepam and oxazepam, which are only conjugated in the liver are subsequently preferred in patients with impaired liver function. In most cases, oral BZDs are sufficient. BZDs should be given in two to four doses per day depending on their half-lives. In the case of delirium tremens or severe symptoms, intravenous administration of BZDs, such as diazepam, is recommended (level A, WFSBP guidelines). Many clinicians favour a symptom-based approach, the optimal dose depends on the severity of AWS and the patient's individual characteristics. BZD monotherapy remains the gold standard for mild and moderate AWS. The CIWA-Ar could help to determine the minimal appropriate dose of BZDs (see also Section 9) (Bhat and Hadley 2015).

In the case of severe or benzodiazepine-refractory AWS, dexmedetomidine (alpha-2 agonist similar to clonidine), propofol or phenobarbital may rarely be

associated to reduce agitation, however propofol may increase the risk of seizures (Mo et al. 2018).

Although no placebo-controlled trials are available, antipsychotics, especially haloperidol, may be used in association with BZDs in the treatment of severe agitation (Mayo-Smith et al. 2004) or psychotic symptoms (Ungur et al. 2013) (Level C, WFSBP guidelines) but the risk of seizures needs to be considered.

Pregabalin, a GABA analogue, at 50 mg/day, has shown some limited success for the treatment of AWS but there have been few randomised studies and a Cochrane review (Leone et al. 2010; Förg et al. 2012 (negative RCT); Freynhagen et al. 2016). Given its potential for misuse or abuse, particularly in subjects with a past history of substance or alcohol abuse, clinicians should exercise caution in this population (Gahr et al. 2013).

Clomethiazole, a thiamine derivative (positive allosteric modulator at the barbiturate site of the GABA-A receptor), which is a potent anticonvulsant hypnotic, is also used in some countries to treat AWS. However, a meta-analysis did not recommend this medication (Level B, Grade 2 according to WFSBP guidelines) (Mayo-Smith et al. 2004).

Anticonvulsants, such as carbamazepine or oxcarbazepine, can alternatively be used to treat AWS (inhibitor of presynaptic voltage-gated sodium channels and glutamate release). A comprehensive review concluded that carbamazepine and oxcarbazepine are efficient in treating moderate-to-severe symptoms of AWS in inpatients (Level B, WFSBP guidelines), but evidence for the prevention of alcohol withdrawal seizures and delirium tremens was inconclusive (Barrons and Roberts 2010) (Level C, Grade 4, WFSBP guidelines). The usual dose of carbamazepine is 600–1,200 mg/day. A retrospective analysis suggested that valproate (inhibitor of voltage-gated sodium channels and histone desacetylases) could be more interesting as compared to carbamazepine in treating AWS (Eyer et al. 2011). However, both carbamazepine and valproate are contraindicated during pregnancy (risk of congenital malformations (Veroniki et al. 2017) and in patients with hepatic or haematological disorders. Gabapentin which inhibits presynaptic voltage-gated sodium and mostly calcium channels, may increase GABA synthesis and interacts with NMDA receptors (Cunningham and Breslin 2004). Gabapentin in higher doses was found to be as clinically effective as lorazepam (Myrick et al. 2009). There is also preliminary evidence that lamotrigine (inhibitor of voltage-gated sodium channels and glutamate release), memantine (NMDA receptor antagonist) and

topiramate (AMPA/kainate receptor antagonist which interacts with GABA-A receptors and voltage-gated sodium and calcium channels) may be useful in the treatment of AWS (Rustembegovic et al. 2002; Choi et al. 2005; Krupitsky et al. 2007) (Level C for topiramate; Level D for lamotrigine and memantine, WFSBP guidelines).

L-Type voltage-gated calcium channel antagonists (diltiazem, verapamil, nimodipine) are probably not effective.

γ -Hydroxybutyric acid (GHB) is a metabolite of the neurotransmitter GABA and it binds to GABA-B receptors (for a review, see Keating 2014; Caputo et al. 2016). The abuse potential of GHB (sodium oxybate (SMO) is the sodium salt of GHB) ('liquid ecstasy') and the risk of severe withdrawal observed with GHB has raised significant concerns regarding its therapeutic use (McDonough et al. 2004; Brennan & Van Hout 2014); however, its potential for abuse remains a controversial topic (Brunt et al. 2014). A Cochrane review does not provide sufficient evidence in favour of GHB (50 mg/day) compared to BZDs and clomethiazole for AWS prevention, but GHB is effective compared to placebo (Leone et al. 2010).

Finally, a recent Cochrane review concluded that the evidence for recommending baclofen, a GABA-B agonist for the treatment of AWS, is insufficient (Level D, Grade 4, WFSBP guidelines) (Liu & Wang 2017).

In summary, BZDs remain the first-line treatment of AWS and delirium tremens in the general population. In Section 12.2.1 we will discuss potential concerns about the use of BZDs during pregnancy.

11.2. Maintenance of abstinence or reduction of consumption

Abstinence from alcohol remains the primary long-term goal for moderate-to-severe AUDs. There is a generally accepted equivalency between alcohol dependence and moderate-to-severe AUDs. However, in patients who are not motivated for abstinence, a reduction in drinking is acceptable. Three medications were approved for the treatment of AUDs by the Food and Drug Administration (FDA; acamprosate, disulfiram and naltrexone) and four in Europe (acamprosate, disulfiram, nalmefene and naltrexone) (for a review of their efficacy, see Soyka et al. 2017). New 2018 American Psychiatric Association AUD guidelines consider acamprosate and naltrexone to be first-line treatments. Disulfiram can be used in those who prefer it or who have failed using the other two. Baclofen was approved in countries such as France but with

caution. SMO (or GHB) was approved in Italy and Austria only. Acamprosate (1.5–2 g/day), naltrexone and disulfiram (125–500 mg/day) are used in patients who are already abstinent from alcohol in order to maintain abstinence. In contrast, nalmefene is used to reduce the level of alcohol use and does not imply previous abstinence. Baclofen may also be used in non-abstinent patients in order to reduce alcohol use and mostly craving.

On the basis of evidence that endogenous opioid peptides, such as β -endorphin, are involved in both the rewarding effects of ethanol and the risk for alcoholism (Gianoulakis 1989; Gianoulakis et al. 1996; Cowen et al. 2004), naltrexone (50 mg/day for 3 months) and nalmefene (10–40 mg/day) have been studied for the treatment of alcohol dependence. Naltrexone is a non-selective antagonist at mu, kappa, and delta opioid receptors. In contrast, nalmefene is not only an antagonist at the mu and delta opioid receptors but also a partial agonist at the kappa opioid receptor (for a review, see Soyka et al. 2017). Naltrexone is available in both oral and long-acting injectable formulations (injectable formulations are available in some countries but not all). There is some evidence that acamprosate (*N*-acetyl homotaurine) acts predominantly via glutamatergic NMDA receptors and is a GABA-A agonist. Disulfiram is an aldehyde dehydrogenase inhibitor that results in a severe reaction when alcohol is consumed concurrently, resulting in a strong deterrent effect.

Treatment with disulfiram is not recommended as first-line treatment despite its potential efficacy (Mutschler et al. 2013; Skinner et al. 2014). SMO or GHB (see also Section 11.2; 50 mg/day) is now widely used to maintain alcohol abstinence in Italy and Austria. According to a Cochrane review, GHB has a better efficacy than naltrexone and disulfiram in maintaining abstinence and has also a better effect on craving than placebo and disulfiram (Leone et al. 2010). However, concern has been raised regarding the development of addiction, misuse or abuse. Baclofen (see also Section 11.2) is a promising anti-craving agent in the treatment of AUDs, its use has increased in some European countries, especially in patients with liver disease (Müller et al. 2015; for a review, see Thompson et al. 2017: 25 studies and 613 patients; dose range: 20–630 mg/day). Side effects have been reported, in most cases at doses over 100 mg/day, they need to be carefully checked.

Palpacuer et al. (2018) conducted a meta-analysis of 32 double-blind RCTs (including more than 6,000 patients) assessing the efficacy of nalmefene,

naltrexone, acamprosate, baclofen or topiramate in non-abstinent adults with AUDs. The primary outcome was total alcohol consumption. Nalmefene (standardised mean difference (SMD), -0.19 ; 95% confidence interval (CI), $-0.29, -0.10$), baclofen (SMD, -1.00 ; 95%CI, $-1.80, -0.19$) and topiramate (SMD, -0.77 , 95%CI, $-1.12, -0.42$) showed superiority over placebo. No efficacy was observed for naltrexone or acamprosate in these studies. No study provided direct comparisons between drugs, but indirect comparisons suggested that topiramate was superior to nalmefene, naltrexone and acamprosate on consumption outcomes. The number of withdrawals for safety reasons increased with nalmefene and naltrexone. Antonelli et al. (2017) also reviewed the safety profiles of these latter compounds.

Otherwise, gabapentin, carbamazepine, valproate and topiramate have been studied to reduce alcohol dependence or to maintain abstinence (for a review, see Ait-Daoud et al. 2006). In general, the results indicated that the randomised evidence for the clinical utility of anticonvulsants to treat AUDs is insufficient. A Cochrane analysis by Pani et al. (2014) assessed the efficacy of anticonvulsants for treating alcohol dependence and concluded that patients treated with topiramate had fewer drinks/drinking days and heavy drinking days and more abstinent days than those receiving placebo. Some guidelines suggested that gabapentin and topiramate showed efficacy and could be used (Reus et al. 2018), they are certainly used extensively clinically in part because they are cheaper.

None of these medications are recommended during pregnancy and lactation (for further details, see Section 12).

12. Management of alcohol use and AUDs during pregnancy and pharmacological treatment options

Considering the severe consequences of alcohol consumption during pregnancy, treatment of alcohol use and AUDs is challenging.

Previous guidelines published in the early 2000s on the management of alcohol use during pregnancy have recommended to reduce maximum levels of alcohol consumption with no risk for low levels up to four units per week (The Royal College of Obstetricians and Gynaecologists UK 2006), or less than seven standard drinks in any week and no more than two standard drinks on any one day (National clinical guidelines for the management of drug use during pregnancy, birth and the early development

years of the newborn, Australian and New Zealand Government, 2006; Australian alcohol guidelines: health risks and benefits. Canberra: NHMRC, 2001: 16. http://www.nhmrc.gov.au/publications/synopses/ds9_syn.htm (accessed September 2006)). However, these recommendations seemed inadequate (Jones et al. 2006; Whitehall 2007). In contrast, in 2002, the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics (Guidelines for perinatal care, 5th ed. Washington, DC: ACOG, 2002: 85) advised its members: 'Women should be dissuaded from alcohol consumption during pregnancy because there is no known safe amount'.

Indeed, whereas most infants with in utero alcohol exposure will not develop FAS, even a moderate amount of alcohol use during pregnancy could represent a risk and no safe threshold for consumption has been identified (see also Sections 5 and 7). Government bodies in various countries and all studies recommend total abstinence from alcohol use for pre-conceptional, pregnant and breastfeeding women (<http://www.iard.org/policy-tables/drinking-guidelines-pregnancy-breastfeeding>), even in women with AUDs. However, little data are available on treatment of AUDs in pregnant women. We found two recent guidelines (Carson et al. 2010); these guidelines were peer reviewed by the principal authors in January 2015 (WHO 2014). We also identified one literature review with recommendations (Bhat and Hadley 2015). The SAMHSA in 2015 and The French Alcohol Society recently published recommendations for pharmacotherapy for alcohol dependence (Rolland et al. 2016) with a small focus on pregnancy. To our knowledge, only the WHO has published specific guidelines intended for the identification and management of substance use and substance use disorders in pregnancy, including alcohol (WHO 2014).

12.1. Evaluation of a pregnant woman with AUDs

In the case of AUDs during pregnancy, information on the quantity, frequency and pattern of consumption should be recorded. The physical examination should evaluate neurocognitive and hepatic function, and identify sequelae of alcohol use. Laboratory testing with blood alcohol levels, blood counts (including MCV), CDT (not always available), testing for vitamin deficiencies, and hepatic (γ GT) and renal testing should be done. Mental health has to be evaluated as well as family and social resources. Comorbid psychiatric disorders should be screened and treated if necessary. Few controlled treatment studies have been conducted in patients with

coexisting psychiatric disorders, a topic that has received more attention in recent years (Odlaug et al. 2016). A history of childhood physical and/or sexual assault was found in between one- and two-thirds of women with substance use disorders; moreover, among women with substance use disorders, studies have found that 30–59% had post-traumatic stress disorder (Bishop et al. 2017). The limited research database indicates that alcohol dependence treatment should be integrated with the treatment of the comorbid psychiatric disorders (Berglund et al. 2003). The quality of relatives and the psychological health of the father should also be evaluated. Social and family supports are also needed. Specialised interviews and speaking groups can be offered. Self help, psychoeducational group are also useful. Group and individual psychotherapy are needed.

For pregnant women who continue to use alcohol during pregnancy, reduction and if possible abstinence must be strongly encouraged (Carson et al. 2010). Pregnant women are often highly motivated to stop using alcohol and many cease alcohol consumption without treatment. However, women with a concurrent diagnosis of substance use disorder may have difficulties to stop alcohol (Bishop et al. 2017). It will be necessary in some women who cannot stop alcohol consumption during pregnancy to arrange referral to addiction treatment services and, if possible, those specialised in perinatology, for a first appointment. A multidisciplinary management should be implemented, with continuous monitoring of the foetus, especially during the third trimester (Bhat and Hadley 2015). Obstetrical monitoring and paediatric surveillance should be anticipating complications at birth or in neonates. A realistic risk reduction programme must be established with all practitioners. BIs may encourage pregnant women to decrease alcohol use; babies born to women in the BI groups showed higher birth weights in some studies (see also Section 10 on BI efficacy in pregnant women).

12.2. Prevention and treatment of AWS during pregnancy

The elevated stress levels induced by alcohol withdrawal could have negative effects on the mother and the foetus due to hypercortisolism (Heberlein et al. 2012). In addition, maternal hypertension may alter the dynamics of the placental circulatory system. Given these risks, the management of alcohol withdrawal in pregnant women warrants a careful and intensive treatment and hospitalisation is recommended (DeVido et al. 2015).

12.2.1. Potential consequences of benzodiazepines' use for prevention and treatment of AWS during pregnancy

BZDs cross the placenta and may bind to receptors in the developing foetal brain. Prenatal exposure to BZDs resulted in behavioural deficits in rats (Kellogg et al. 1980) and to potential negative consequences in humans (Sutter-Dallay and Riecher-Rössler 2016).

Consequences of BZDs use during the first trimester of pregnancy.

In humans, BZD use during the first trimester of pregnancy has been associated with an elevated risk of oral clefts and other malformations, with controversial results due to differences in methodological approaches. Diazepam and chlordiazepoxide were among the drugs most frequently implicated in the earlier studies (Saxen and Saxen 1975; Dolovich et al. 1998; Enato et al. 2011). The type of BZDs, the dosages used, gestational age at exposure and concurrent substances used were not clearly analysed in many studies. In contrast, data from other studies provide no clear evidence of significant increase in either the overall incidence of malformations or of any particular type of defect (McElhatton 1994). According to McElhatton (1994), many of the women included had comorbid psychiatric illnesses or somatic diseases, which may have increased the risk, and some women were also on multidrug therapy. In addition, medical-obstetric histories and family history of malformations were not always taken into account. Yet, using the French Central East registry of congenital malformations (1976–1997), a significant association was reported between lorazepam and anal atresia (OR = 6.2; 95% CI, 2.4–15.7; $P = 0.01$) (five cases among six malformations were exposed to lorazepam during foetal life) (Bonnot et al. 2003). In this latter study, in 262 cases, BZD use was reported during the first trimester of pregnancy. Similarly, an increased risk for alimentary tract atresia (oesophageal or anal) or pyloric stenosis was described in another study (especially with alprazolam and diazepam) (Norstedt Wikner et al. 2007). Alprazolam was also associated with cardiovascular defects (mainly septum defects) (Källén et al. 2013).

In summary, chlordiazepoxide and diazepam (with caution) should be considered first-line BZDs when needed in early pregnancy (Iqbal et al. 2002; Bellantuono et al. 2013). Some caution is given with clonazepam and lorazepam due to higher malformation risks. However, these risks remain low (less than 1%). Data on alprazolam, nitrazepam and medazepam are still too scarce to conclude (Bellantuono et al.

2013), but some caution exists with alprazolam. The scale CIWA-Ar could be helpful to determine the minimum dose of BZDs required (see also Section 9). Yet, no studies or case reports have been published considering the use of CIWA-Ar during pregnancy; moreover, some symptoms of alcohol withdrawal could be confounded with symptoms due to pregnancy (Bhat and Hadley 2015).

Consequences of BZDs use during the third trimester of pregnancy. Maternal use of BZDs during late pregnancy (but sometimes earlier) was also associated with neonatal morbidity, an increased risk of preeclampsia and haemorrhage around delivery, preterm birth, low birth weight and height. A low Apgar score, an increased risk of hypoglycaemia and respiratory and neurological problems were also reported. Yonkers et al. (2017) in a cohort of 2,654 pregnant women reported that maternal BZD use (67 cases, mostly during early pregnancy) was associated with caesarean delivery (OR: 2.45), preterm birth (OR: 1.98), low birth weight (OR: 3.41), and use of ventilatory support for the newborn (OR: 2.85), but neither panic disorder (98 cases) nor generalised anxiety disorders (252) was associated with these maternal or neonatal complications (tobacco, alcohol and illicit drug use were also taken into account in the statistical analyses). In the same way, Calderon-Margalit et al. (2009) reported increased odds of preterm birth (OR: 6.8), lower birth weight and respiratory distress syndrome at birth with the use of BZDs during pregnancy. However, there has been no significant increase in the incidence of neonatal jaundice and kernicterus after birth. Moreover, some infants exposed to BZDs during the late foetal period exhibit either floppy infant syndrome (Gillberg 1977) or marked neonatal withdrawal symptoms (Rementeria and Bhatt 1977). Floppy infant syndrome varies from mild sedation, hypotonia and reluctance to suck, to apnoeic spells, cyanosis and/or impaired metabolic responses to cold stress. These symptoms can persist from hours to months after birth. This correlates well with the pharmacokinetic and placental transfer of BZDs. Neonatal BZD withdrawal can include symptoms such as hypertonia, hyperreflexia, restlessness, irritability, abnormal sleep patterns, inconsolable crying, tremors, bradycardia, cyanosis, suckling difficulties, apnoea, diarrhoea and vomiting, as well as growth retardation. In neonates, these symptoms can be easily missed or sometimes be confused with other disorders. High medication dosages (equivalent to diazepam >30mg/day), especially with long half-life BZDs, such as nitrazepam and diazepam, were associated with the highest

risk, whereas short half-life BZDs, such as oxazepam and temazepam, were not associated to toxicity in most cases (Kieviet et al. 2013). However, DeVito et al. (2012) reported that, 'no studies suggested that using a long-acting (i.e., clonazepam) versus a short-acting (i.e., lorazepam) BZD reduces the risk of developing either floppy infant syndrome or neonatal BZD withdrawal'. Interestingly, oxazepam has a favourable pharmacokinetic profile with intermediate half-life and no active metabolites. Even if little data are available, oxazepam should be the BZD with the highest interest in alcohol withdrawal in pregnant women.

Developmental effects observed after prenatal exposure to BZDs. Results on mental health outcomes in the offspring after prenatal exposure to BZDs have been conflicting. A sibling-matched study found no association with behavioural deviation in ten children at age 8–12 months after acute prenatal exposure to medazepam used for self-poisoning alone or with other drugs between the 4th and 12th postconceptional weeks (Gidai et al. 2008). In contrast, Viggedal et al. (1993) showed reduced personal-social behaviour abilities at 1.5 years in 17 children exposed to BZDs during foetal life, but found that externalising problems such as hyperactivity or attention problems were not significantly different from controls (born to mothers who had not used psychoactive substances or BZDs). In the prospective study by Laegreid et al. (1992), at 18 months, 17 BZD (only)-exposed children showed more frequent deviations in muscle tone and pattern of movements, with impaired fine motor functions, than 29 non-exposed children. There was also a slightly decreased head circumference and, in five cases, craniofacial anomalies. A retrospective study based on 15 exposed children (mothers have used diazepam during the second half of their pregnancy) found no effects on behaviour at the age of 9–10 years compared to non-exposed children (Stika et al. 1990). Another study that followed up 550 children up to 4 years of age, exposed to BZDs in utero, showed no increase in either the malformation rate or adverse effects on neurobehavioral development or intelligence quotient (McElhatton 1994). Although some data indicate that a small number of children were slower to develop during the first year, they caught up in terms of growth, and most had normal development by 4 years of age according to the scales used. Where developmental deficits persisted, a causal relationship with BZD exposure could not be reported (poor environment or social factors were also associated). Finally, in a prospective follow-up study, Brandlistuen et al. (2017) compared 315 children who

received BZDs during foetal life with non-exposed siblings (108 cases). Long-term (≥ 2 pregnancy periods) prenatal exposure to benzodiazepine anxiolytics, was associated with increased internalising problems in the exposed child (i.e., anxiousness, emotional reactivity or somatic complaints), lasting up to 3 years of age. These latter findings could not be explained by shared familial environment, indication for use or other measured factors.

In summary, data concerning the teratogenicity of BZDs are controversial. Late BZD use (third trimester) or exposure during labour seems to be associated with greater risks to neonates. In addition, prolonged use of BZDs throughout pregnancy raised concerns about alteration of neurotransmitter synthesis and function leading to postnatal developmental or behavioural problems. When assessing the prenatal influence of BZDs on child development, it is always difficult to disentangle maternal illness requiring BZD use, BZD potential toxicity and social factors. For all these reasons, it seems reasonable to avoid BZDs for the treatment of alcohol withdrawal during pregnancy unless the severity of the withdrawal symptoms would expose the foetus to a greater risk compared to the risk associated to BZDs use for 1 week during pregnancy. Oxazepam may have a better risk/benefit ratio.

According to the FDA classification, all BZDs were classified D during pregnancy, which means that caution is required in their use during pregnancy (except for oxazepam which was not classified due to little data).

Pregabalin. Pregabalin exposure during pregnancy might be associated with major birth defects, whereas the rate of spontaneous abortion was not increased (Winterfeld et al. 2016). Mostacci et al. (2018) reported that, among 30 pregnancies exposed to pregabalin only (among more than 145,000 pregnancies studied retrospectively), the rate of spontaneous abortion or preterm birth was twice that observed in non-exposed pregnancies (exposure was based on reimbursed prescription databases). Among the 13 newborns exposed to pregabalin during the first trimester, one has a ventricular septal defect.

Pregabalin was classified into category C by the FDA; however, pregabalin is not recommended in pregnant women for the treatment of AWS.

12.2.2. Chlormethiazole is not recommended for prevention and treatment of AWS during pregnancy

Chlormethiazole is used in Central Europe; teratogenicity was not reported in the 1960s but studies in pregnant women are lacking (Lechat 1966).

12.2.3. Anticonvulsants are not recommended for prevention and treatment of AWS during pregnancy

An increased risk for congenital malformations was observed for nearly all first-generation anticonvulsants in infants exposed to anticonvulsants in early pregnancy: CNS defects, congenital heart defects, diaphragmatic hernia, hypospadias, per equinovarus and orofacial clefts were described. According to a review conducted by Wlodarczyk et al. (2012), the most common malformations observed with in utero use of anticonvulsants were cardiac malformations followed by hypospadias and oro-facial clefts. Neural tube defects, alimentary tract atresia or stenosis, severe renal malformations, and craniostenosis were also reported in a Swedish medical register. In addition, certain anticonvulsants (e.g., valproic acid) were associated with specific types of malformations such as a 1–2% risk of neural tube defects (especially spina bifida), which means a 10–20-fold increased risk; carbamazepine was associated to a 0.5% risk (Veroniki et al. 2017). Regarding valproate, neurodevelopmental deficits, reduced verbal abilities and poorer attentional tasks with inconclusive effectiveness of folate supplements regarding prophylaxis of malformations were also reported (Jentink et al. 2010; Gentile 2014), which precludes its use during pregnancy. Monotherapy carried less risk for teratogenesis than polytherapy (for a review, see Källén et al. 2013). In general, among anticonvulsants, the highest risk was observed with valproic acid and the lowest with lamotrigine.

Yet, concerning the newer drugs, data regarding lamotrigine are controversial. Most studies reported no increased risk for major congenital malformations, whereas one study reported a dose–response risk of oral facial clefts (above 300 mg/day) (Holmes et al. 2008). A significantly higher prevalence of anencephaly (three cases) and an increased frequency of cardiac heart defects (compared to the reference database) were reported with lamotrigine, but an association was not concluded because these findings were not supported by other studies (Cunnington et al. 2011; De Jong et al. 2016). Lamotrigine was classified into category C by the FDA.

The same risks were associated with topiramate, even if three cases of normal infants born to a mother who had been receiving topiramate during gestation were reported (Morrell 1996). Topiramate was associated with a substantial risk of foetal growth restriction, and possibly an increased malformation rate; infants exposed to topiramate had a considerable risk of microcephaly (11.4 vs 2.4%) and lower birth weights (24.4 vs 8.9%) (Veiby et al. (2014), control group of

non-exposed pregnancies and non-treated epileptic pregnant women). There is also a strong indication of an association between cleft lip with or without cleft palate and a higher risk of hypospadias with topiramate monotherapy in the first trimester of pregnancy (for a review, see de Jong et al. 2016). Topiramate was classified into category D by the FDA, considering data reporting an increased risk for oral clefts.

Animal studies have revealed evidence of fetotoxicity with gabapentin involving delayed ossification in several bones of the skull, vertebrae, forelimbs and hindlimbs. Hydroureter and hydronephrosis have also been reported in animal studies. Morrow et al. (2006) and Mølgaard-Nielsen and Hviid (2011) reported two cases of congenital heart disease in newborns exposed to gabapentin. A slightly higher risk of preterm birth and low birth weight after intrauterine exposure to gabapentin was reported by Fujii et al. (2013), but the risk of major malformations was not increased (women were receiving gabapentin for pain, epilepsy or psychiatric disorders in association with other psychotropic drugs). There have been no controlled studies in human pregnancy (Mostacci et al. 2018). Gabapentin was classified as C by the FDA during pregnancy.

Finally, an increased risk of preterm birth, low birth weight, small head circumference and neonatal complications (respiratory, hypoglycaemia and neurological symptoms) was observed with maternal use of anticonvulsants during the second and third trimesters of pregnancy, but the strongest effects were observed with valproic acid and carbamazepine (Källén et al. 2013).

In summary, the teratogenic effect of many anticonvulsants precludes their use during pregnancy, especially for valproic acid and carbamazepine, which must be avoided.

12.2.4. Folic acid and vitamin B1 supplementation during pregnancy

Periconceptional folic acid supplementation (0.4 mg/day) effectiveness regarding prophylaxis of congenital malformations associated to the use of anticonvulsants during pregnancy is controversial (Yerby 2003; Ornoy and Ergaz 2010). Patients with alcohol abuse often suffer from B vitamin deficiencies; oral thiamine (vitamin B1) daily is prescribed during the detoxification period. Vitamin B1 crosses the placenta. However, little is known on its use and safety profile during pregnancy (Rayburn and Bogenschutz 2004).

12.3. Maintenance of abstinence or reduction of alcohol use (pharmacological treatment) during pregnancy

12.3.1. Acamprosate

Preclinical studies suggested possible teratogenic effects with a dose-related increase in the number of fetuses with malformations in rats at oral doses of 300 mg/kg/day or greater (approximately equal to the maximum recommended human daily oral dose). The malformations included hydronephrosis, malformed iris, retinal dysplasia, and retro-oesophageal subclavian artery (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4530607/pdf/nihms705835.pdf>). There are no adequate or well-controlled studies in pregnant women.

Acamprosate was classified into category C during pregnancy by the FDA.

12.3.2. Naltrexone

Since the endogenous opioid system is active during foetal development, the long-term effects of opioid system antagonism are still very much unknown, mu opioid receptors may be altered (Helmbrecht and Hoskins 1993; Zagon et al. 1998). McLaughlin et al. (1997) reported that offspring exposed to naltrexone prenatally had higher body weights and length as well as organ weights at post natal day 21. Prenatal naltrexone may also facilitate masculine behaviour in offspring of rats (Cohen et al. 1996). Interestingly, maternal naltrexone treatment prevents morphological and behavioural deficits induced in rats by maternal stress (Keshet et al. 1995). Finally, significant alterations in morphine-induced neuroplasticity and increased risk of opioid abuse later in life were observed in offspring of female rats exposed to naltrexone during pregnancy (Farid et al. 2012).

Although, in humans, naltrexone has been employed during pregnancy without notable adverse effects, there has been no long-term follow-up study (Hulse et al. 2001). Several studies suggested good tolerability in opioid-dependent pregnant women (Saia et al. 2016). Compared with a control group (569 neonates, born from non-opioid-dependent women), naltrexone-exposed neonates ($n=68$) (used in the treatment of pregnant opioid-dependent women) were not significantly different in terms of congenital anomalies, stillbirths and mortality; in contrast, they had significantly lower birth weights (significantly superior to the methadone group but not different from the buprenorphine group), spent more time in hospital after birth (5.5 vs 4.3 days in the control

group compared to 11.3 in the methadone group ($n = 199$) and 8 in the buprenorphine group ($n = 124$), and had higher rates of neonatal abstinence syndrome (7.5 vs 0.2% in controls compared to 51.5 in the methadone group and 41.8% in the buprenorphine group) (Kelty et al. 2017). This was a retrospective study using state records of neonates born between 2001 and 2011. These latter findings are difficult to analyse due to the potential confounding effects of opioid addiction in these pregnant women.

Naltrexone was classified into category C during pregnancy by the FDA.

12.3.3. Nalmefene

There was no evidence of impaired fertility or harm to the foetus. There are, however, no adequate and well-controlled studies in pregnant women (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=49fd02f8-12b8-460c-ae1f-f26738d86998>).

Nalmefen was classified into category B during pregnancy by the FDA, despite little data.

12.3.4. Baclofen

It has a low molecular weight, is hydrophilic with low protein binding (30%), which confers an important potential for transplacental transfer and a prolonged half-life as a result of immature renal and metabolic functions (Chasnoff 2003). Baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) and incomplete sternebral ossification, in foetuses of rats given approximately 13 times the maximum recommended human dose, as well as the incidence of unossified phalangeal nuclei of forelimbs and hindlimbs in foetuses of rabbits given approximately seven times the maximum recommended human dose. In contrast, in mice, no teratogenic effects were observed, although reductions in mean foetal weight with consequent delays in skeletal ossification were present when given 17 and 34 times the human daily dose.

In humans, 134 pregnant women who received baclofen in early pregnancy (between weeks 4 and 12) (for neurological disorders with less than 30 mg/day in half of cases; eight women were receiving higher doses for alcohol addiction (median 85 mg/day)) were compared to 400 pregnant controls (non-exposed to baclofen) (Bernard et al. 2014; Prescrire Int. 2015). The rates of spontaneous miscarriage were similar but pregnancy terminations were more frequent in the baclofen group (14.9 vs 4.2%), and the odds ratio of major malformations was 4.1 (five of 104 newborns in the baclofen group versus four of 330 in the non-exposed group,

including: anencephalia; subumbilical omphalocele with a posterior fossa cyst, cervical hygroma and club feet; a tracheal cavernous haemangioma; malformation of kidneys; oral cleft). Moreover, convulsions, sedation and withdrawal symptoms have been reported among newborns of mothers who had taken baclofen during late pregnancy (second and third trimesters) (Bernard et al. 2014; Prescrire Int 2015; Freeman and Delawey 2016 (one case report)). In additional case reports, one neonate (at the 7th day) required baclofen therapy to control unresponsive generalised seizures to conventional treatment, following maternal exposure (a paraplegic mother) to oral baclofen (80 mg/day) (Ratnayaka et al. 2001). Moran et al. (2004) reported another neonate who developed withdrawal symptoms shortly after birth (the mother was receiving baclofen at 20 mg/day for the treatment of reflex sympathetic dystrophy, she was also receiving clonazepam and oxycontin). Duncan and Devlin (2013) reported hypertonicity, abnormal sleep patterns, fever and loose stools in a preterm infant whose mother was receiving 90 mg/day of baclofen for the treatment of spasticity associated to paraplegia (no past history of drug use and no other treatment). In contrast, in two cases, exposure to baclofen during pregnancy (maternal doses between 25 and 30 mg daily) resulted in normal neonatal outcome (Weatherby et al. 2004; Goldkamp et al. 2011).

FDA considered baclofen into category C for use in pregnancy. Yet, clinicians must be aware of the risk of severe withdrawal symptoms including convulsions at birth.

12.3.5. Disulfiram

There is some evidence suggesting an increased risk of congenital malformations associated with the use of disulfiram in the first trimester of pregnancy. In a women exposed to cocaine, cannabis, alcohol, tobacco and disulfiram during the first trimester of pregnancy, female monozygotic twins were discordant for congenital anomalies (reduction defect of the right forearm in one case and cleft palate in the other one, respectively). Both were small for gestational age (Reitnauer et al. 1997). Limb reduction anomalies were also reported by Nora et al. (1977) in exposed neonates. Dehaene et al. (1984) reported Pierre Robin syndrome in a newborn infant whose mother had been exposed to disulfiram during pregnancy. Another severely malformed and mentally retarded child was reported whose previously alcoholic mother had been receiving disulfiram during early pregnancy, but denied alcohol intake (Gardner and Clarkson 1981). In contrast, Helmbrecht et al. (1993) reported normal

outcomes in neonates exposed to disulfiram during the first trimester of pregnancy. Yet, the Canadian Mother-Risk Program classified disulfiram (in line with valproic acid) as a drug of concern during pregnancy as early as 1988 (Bologa-Campeanu et al. 1988).

In addition, the degree of the disulfiram-alcohol reaction may induce severe acute autonomic instability, resulting in a hypertensive response which may also be considered as a risk to the pregnant woman and her foetus (DeVido et al. 2015). Unfortunately, no studies have been reported on the assessment of this particular risk. In addition, copper is known to play a key role in the process of formation of neurons and neuronal migration, and thus disulfiram should be avoided at any time during pregnancy because of its potent copper-chelating characteristics (Saxon et al. 1998; Chick 1999).

Disulfiram was classified into category C during pregnancy by the FDA but should not be used because of risk of disulfiram reaction. It was considered as a drug of concern during pregnancy in Canada.

12.3.6. SMO or GHB

The abuse potential of GHB and the risk of severe withdrawal observed with GHB have raised significant concerns regarding its therapeutic use during pregnancy (McDonough et al. 2004; Brennan & Van Hout 2014). There are no adequate data on the developmental risk associated with the use of SMO in pregnant women. Oral administration of SMO to pregnant rats resulted in increased stillbirths and decreased offspring postnatal viability and growth, at a clinically relevant dose (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=926eb076-a4a8-45e4-91ef-411f0aa4f3ca#section-8.1>).

Despite its potential for abuse and little data, SMO was considered C by the FDA.

In summary, none of these latter pharmacological treatments can be recommended during pregnancy, as there is insufficient evidence concerning their safety including the risk of malformations and withdrawal symptoms at birth, as well as the subsequent risk of opioid abuse with opioid antagonists.

12.4. Post-partum care of women with AUDs during pregnancy/breastfeeding

After birth, health professionals have to be aware of the newborn's medical condition, including the risk of FASD, withdrawal or intoxication syndrome. Prolonged hospitalisation in obstetrics or mother-baby units (where mothers and babies are hospitalised together)

can be provided if necessary. Skin-to-skin contact with the newborn must be promoted as in any birth. The father must be included in the care of baby and mother.

Prenatal alcohol exposure is a leading preventable cause of birth defects and developmental disabilities. Subsequently, careful screening for FASD must be carried out at birth and regularly thereafter during the first years of development. In the case of any doubt of foetal alcohol exposure, alcohol metabolites, such as EtG or FAEE, must be measured in the meconium at birth (Lamy et al. 2017). Unfortunately, the diagnosis of FASD is usually made after birth, sometimes only at adult age when alcohol damage has become irreversible and permanent.

In all women with alcohol consumption, early prenatal care should be implemented in a multidisciplinary management. Networking between psychiatrists, gynaecologists and obstetricians, paediatricians, GPs, midwives and social care services is essential. Follow-up by a team specialised in perinatal psychiatry, initiated during pregnancy, must be continued in the post-partum period with educational and preventive interventions of health professionals (i.e., home visits of professionals, consulting with a psychologist or a psychiatrist specialised in perinatal care, etc.). Particular attention must be paid to the quality of the early relation with the baby; fathers should be included in this relation. Extended support should help the mother in caring for her baby, support her in early interactions and thus reduce the risk of neglect or abuse of the child. In case of professional concerns (carelessness, mistreatment, inconsistency of interactions, etc.), temporary measures for the child can be put in place to protect him or her.

The post-partum period is also a vulnerable time for relapse of alcohol use and continuing follow-up, as well as identifying risk factors for relapse, can help prevent relapse and improve future pregnancy outcomes (Barlow et al. 2015). BIs may be helpful in reducing psychological distress (Fleming et al. 2010). Specific psychosocial and medico social care may also help to decrease risk factors for relapse such as comorbid somatic or psychiatric disorders, domestic violence, homelessness, etc.

During this post-partum period, the available guidelines about AUDs may apply (see Guelinckx et al. 2011; Soyka et al. 2017).

Breastfeeding is neither recommended in the case of alcohol use (increased risk of alcohol spectrum disorders (May et al. 2016)) nor during pharmacological treatment used to maintain alcohol abstinence. Both the animal

Table 2. Level of evidence of intervention according to the available literature.

Type of intervention		Category of evidence
<i>Preconception</i>		
Preconceptional screening in pregnant women	Risky or high prepregnancy drinking is a strong predictor of alcohol use during pregnancy	B
Brief Intervention efficacy in preconceptual women		A/B
<i>Pregnancy</i>		
Recommendations concerning alcohol use during pregnancy	Abstinence in alcohol use is recommended in all pregnant women	B
Screening in pregnant women	Self-report	Self-report: alcohol use is under-reported during pregnancy Assessment per se may have a positive effect on risky drinking
	Rating scales	AUDIT-C TWEAK T-ACE
Brief interventions (short versions of CBT and/or motivational interviewing)		Patient-centered counselling sessions with a trained professional (5 min of brief advice to 15–30 min of brief counselling) (face-to-face or by phone)
		Self-applied interventions (manuals or computer-based tools)
		Specific programmes for pregnant women
<i>Alcohol withdrawal treatment</i>		
Hospitalization	Recommended in the case of high and chronic alcohol use	B/C
Type of pharmacological treatment	No specific studies in pregnant women	D
Maintenance of abstinence or reduction of alcohol use	No specific studies in pregnant women	D
Breastfeeding	In the case of alcohol use or of pharmacological treatment used to maintain abstinence (lack of studies)	D
FADS diagnosis		Systematic search in the case of any doubt of alcohol use during pregnancy
		Alcohol metabolites should be measured in meconium of neonates

and human literature indicate that early experiences with neonatal alcohol exposure can exert short- and long-term effects upon subsequent alcohol responsiveness in terms of facilitating later recognition, discrimination and even acceptance of the drug's chemosensory properties (Molina et al. 2007). This is important because these early life experiences may reveal a high predisposition for alcohol ingestion in the future.

13. Guidelines for the treatment of alcohol use and AUDs in pregnant women

13.1. Level of evidence of intervention according to the available literature (Table 2)

See also [Supplementary Table 1](#) which explains the categories of evidence and recommendation grades used in [Table 2](#) (Bandelow et al. 2008).

Table 3. Guidelines for pharmacological treatment of AUDs during pregnancy.

Type of intervention	Type of treatment	Recommendation
<i>Alcohol withdrawal treatment</i>		
	BZDs	D for: alprazolam, lorazepam, clonazepam, diazepam and chlordiazepoxide C for oxazepam but few data
	Pregabalin	D
	Anticonvulsants	Valproate* and carbamazepine are contraindicated D for others C for Lamotrigine
	Baclofen	D (risk of withdrawal at birth)
	SMO or GHB	D (risk of withdrawal at birth)
<i>Maintenance of abstinence or reduction of alcohol use</i>		
	Acamprosate	C
	Naltrexone	C
	Nalmefene	C (lack of data)
	Baclofen	D (risk of malformations, convulsions at birth)
	Disulfiram	D (drug of concern)
	SMO or GHB	D (risk of withdrawal at birth)
<i>Breastfeeding</i>		
	Alcohol use	Contraindicated
	Pharmacological treatment (maintenance of abstinence)	Contraindicated

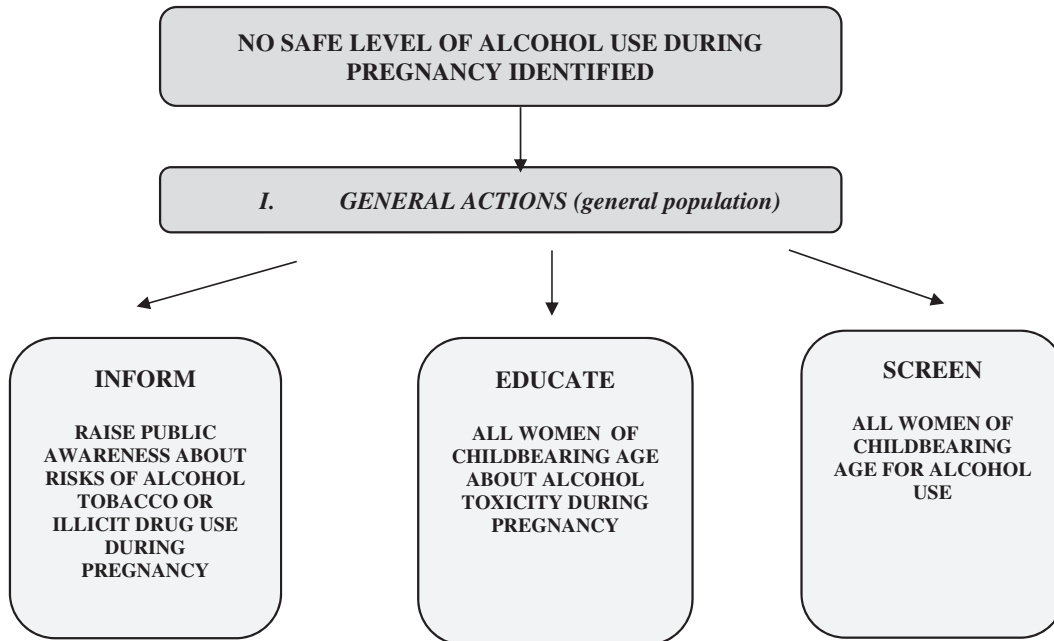
*Valproic acid is an acid. Its conjugate base is valproate. The sodium salt of the acid is sodium valproate and the coordination of both is valproate semisodium.

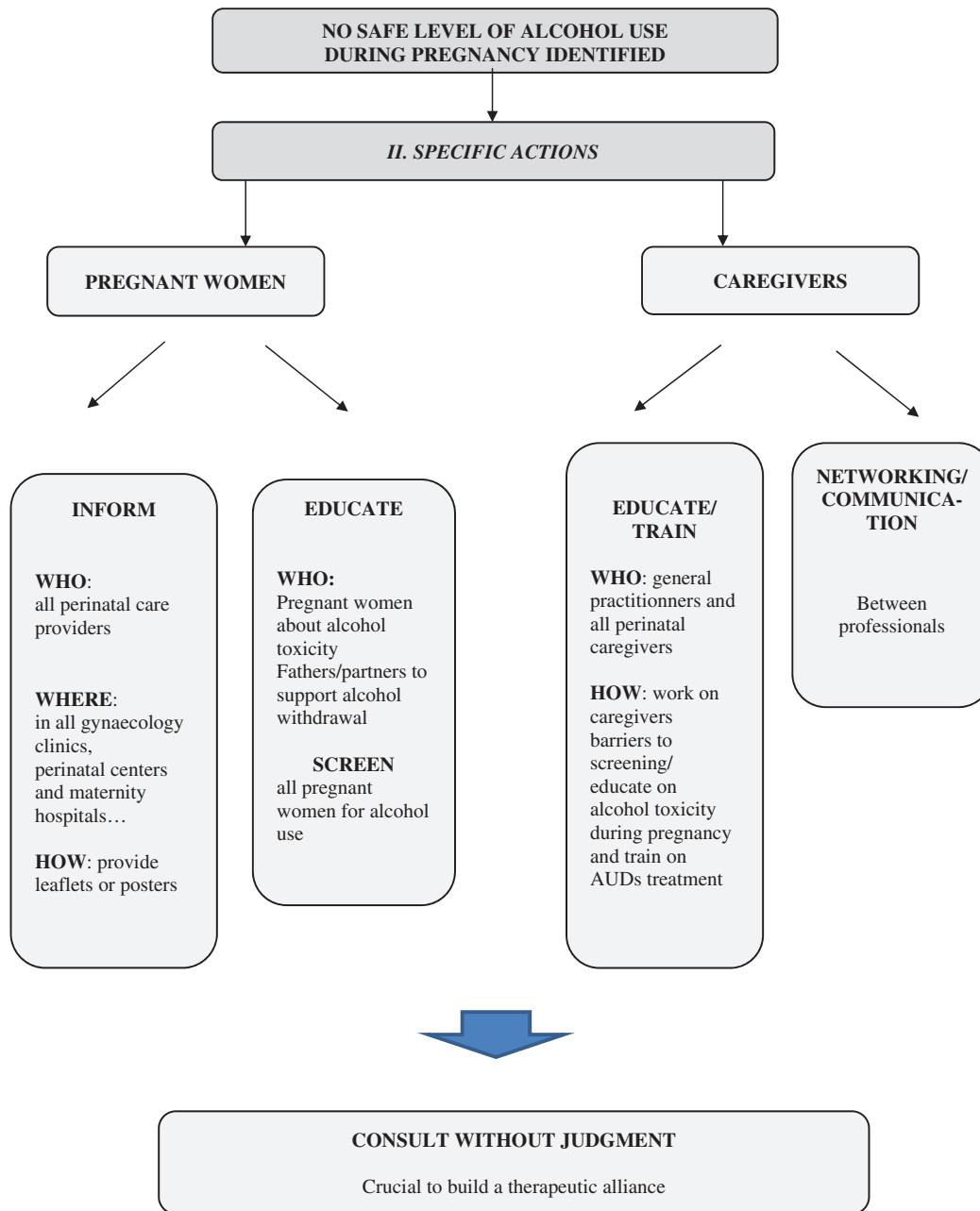
13.2. Guidelines for pharmacological treatment of AUDs during pregnancy (Table 3)

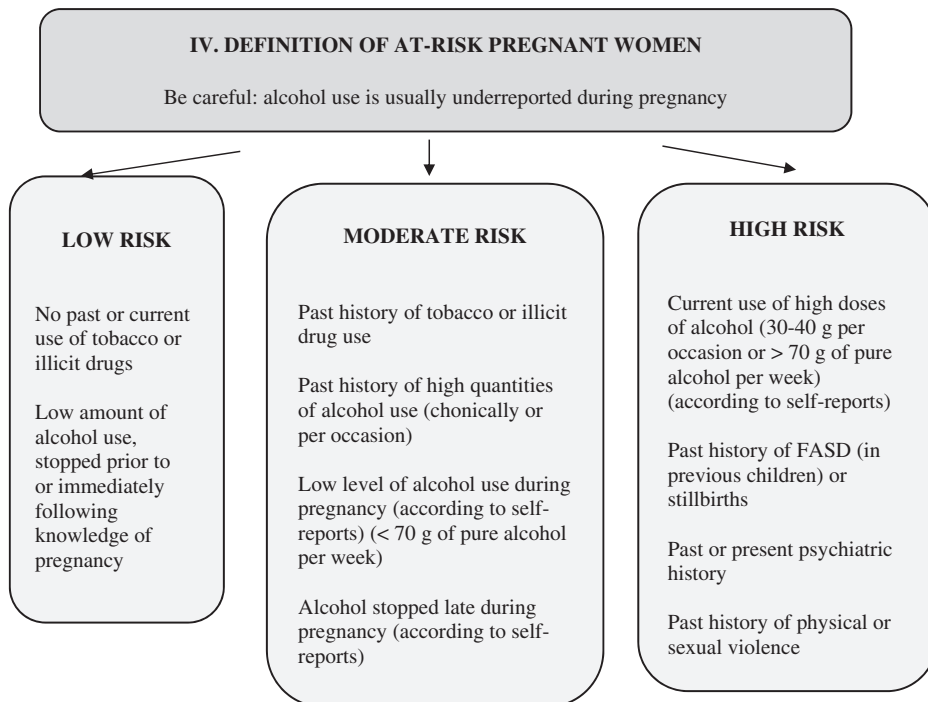
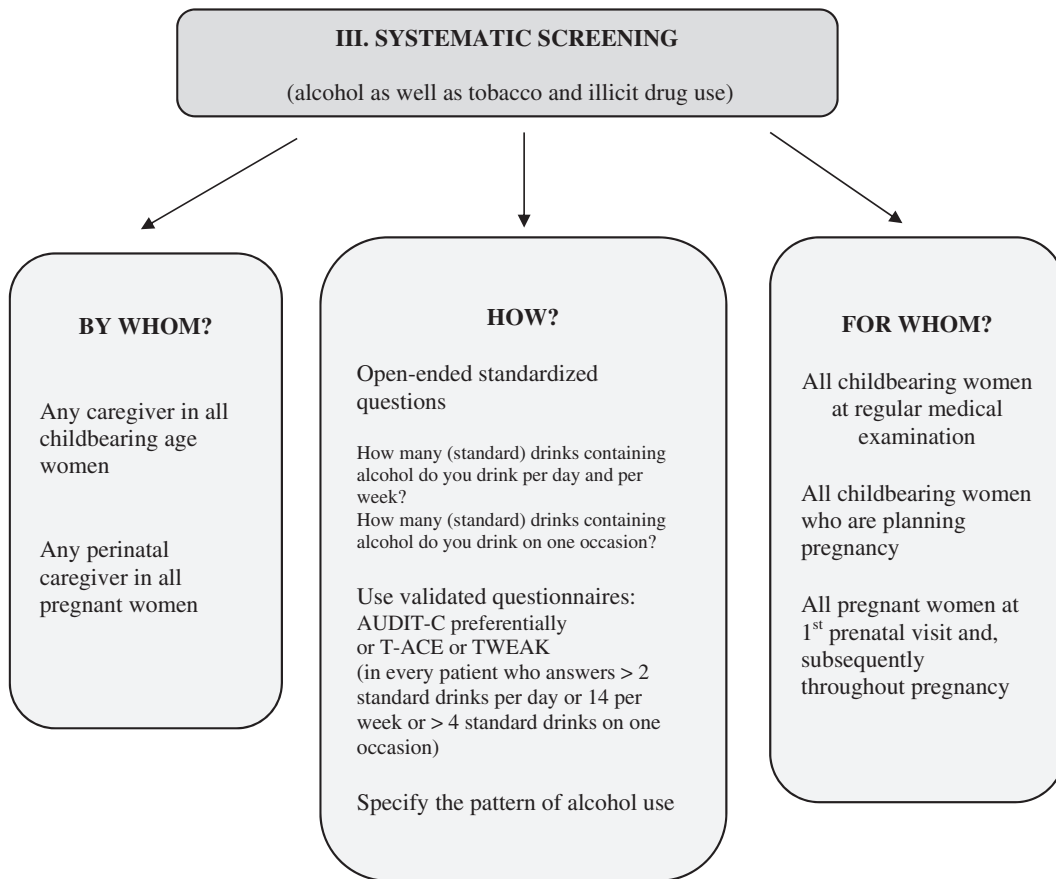
Legend: A, no evidence of risk in preclinical as well as clinical studies SAFE; B, no risk in preclinical studies, lack of data in pregnant women RELATIVELY SAFE; C,

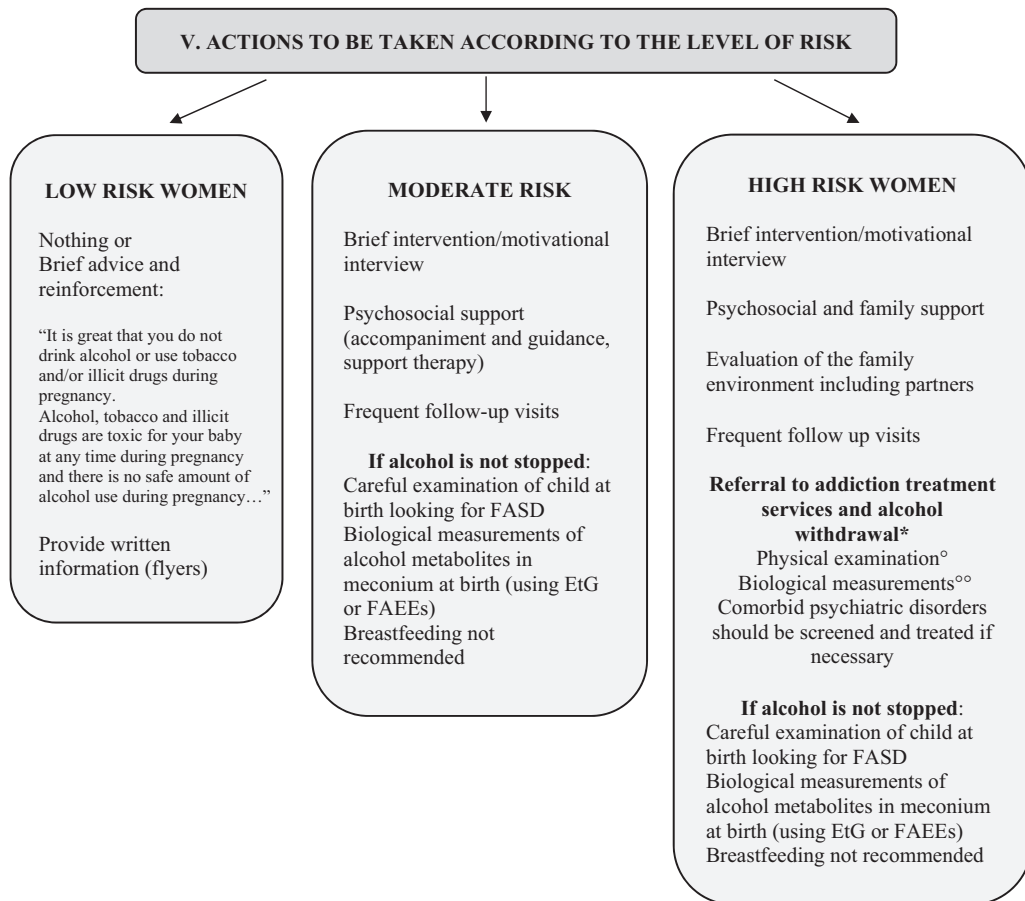
adverse effects in preclinical studies, lack of data in pregnant women CAUTION; D, adverse effects in pre-clinical studies and in pregnant women AVOID.

13.3. Summary of the guidelines





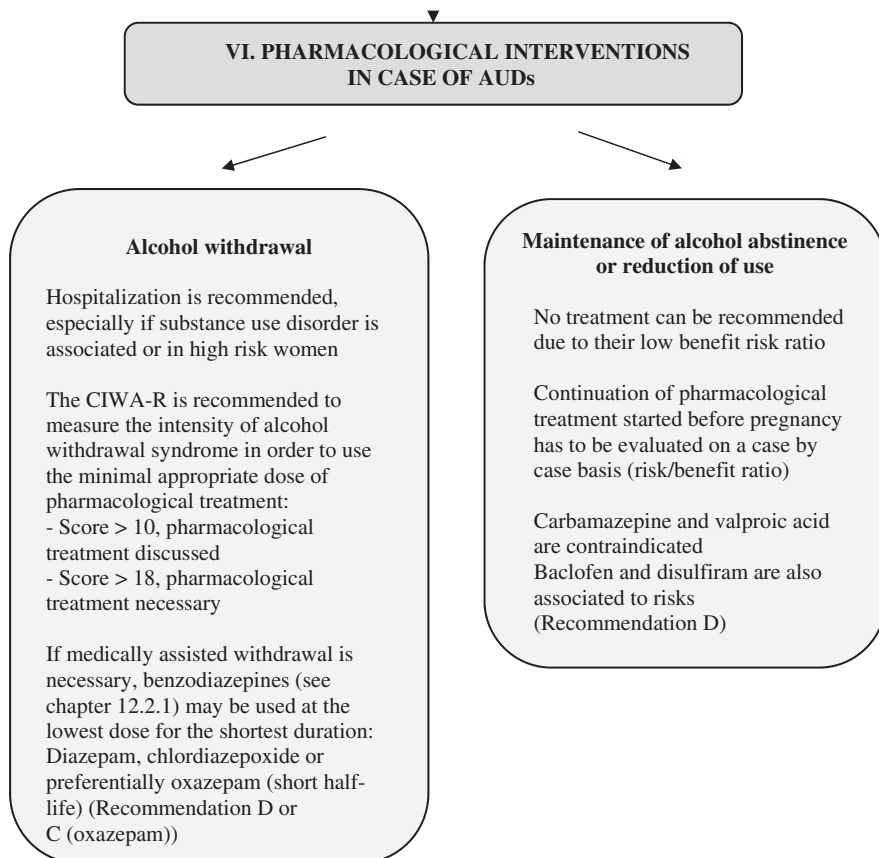




*If possible specialized in perinatology for a first appointment

[°]Assess neurocognitive and liver functions evaluating sequelae of alcohol use

^{°°}Blood alcohol levels, blood counts, testing for vitamin deficiencies, CDT, hepatic and renal testing



**VII. DELIVERY and POST PARTUM PERIOD
IN AT-RISK WOMEN**

ANTICIPATE obstetric and paediatric monitoring

EXAMINE neonates looking for FASD

MAKE biological measurements of alcohol metabolites in meconium (using EtG or FAEEs)

SEARCH for withdrawal or intoxication symptoms

PROMOTE mother/baby contact AND INCLUDE fathers/partners

PROLONG hospitalization in specialized units (mother-baby units) if needed

AVOID breastfeeding

In case of alcohol exposure during pregnancy:

FOLLOW-UP by a team including pediatricians and psychiatrists specialized in perinatal psychiatry must be continued in the post partum period and during childhood

14. Conclusion

There is no safe level of alcohol use during pregnancy and abstinence is recommended. There is very little evidence based on the literature for screening and management of alcohol use during pregnancy and for the treatment of AUDs in pregnant women. All perinatal caregivers should be aware of foetal problems related to alcohol use during pregnancy (such as FASD or birth defects) as well as of risks associated with pharmacological treatment used for AUDs.

Public awareness about the risks of alcohol, tobacco and illicit drug use during pregnancy should be raised; all childbearing age women must be informed about their potential harm in the case of prenatal exposure. Ideally, women should stop alcohol use when pregnancy is planned and, in any case, as soon as pregnancy is known.

Detecting patterns of maternal alcohol drinking during pregnancy at first antenatal visit and throughout pregnancy with or without rating scales is critical to prevention of FASD. Pregnancy is a window of opportunity for addressing alcohol, and also tobacco or illicit drug use, as the vast majority of pregnant

women are interested in giving birth to a healthy baby. In this context, pregnant women may already have a strong motivation to stop or decrease alcohol use which may favour the effectiveness of BIs in the case of low-to-moderate risk of alcohol use.

Education and training regarding screening and management of alcohol use in pregnant women should be promoted in all perinatal caregivers. Pregnant women tend to under declare alcohol consumption, and perinatal caregivers are in an ideal position to screen pregnant women for alcohol use and to advise women on the importance of avoiding alcohol. They can use BIs or refer them to specialised treatment units if necessary (depending of the level of risk of AUDs). Networking and communication between health professionals during pregnancy and delivery as well as after birth should be improved.

Low doses of BZDs (Recommendation D) may be used if necessary, at the lowest dose and for the shortest duration, to prevent alcohol withdrawal symptoms when chronic and high alcohol intake is stopped. The CIWA-R is recommended to measure the

intensity of AWS in order to use the minimal appropriate dose of pharmacological treatment.

Due to the low level of evidence or to their low benefit/risk ratio, pharmacological treatment for maintenance of abstinence should not be used during pregnancy. Furthermore, carbamazepine, and especially valproic acid, are contraindicated during pregnancy. Caution is required if baclofen or SMO are used during pregnancy and disulfiram should be avoided.

At birth, screening for FASD must be carried out, and alcohol metabolites should be measured in meconium of neonates if there is any doubt of foetal alcohol exposure.

Fathers or partners should be included as much as possible in pregnancy care, withdrawal of tobacco, alcohol and illicit drug use as well as in prenatal/infant care and education.

The post-partum period is also a vulnerable time and continuing follow-up as well as identifying risk factors for relapse can help prevent relapse and improve future pregnancy outcomes. In the post-partum period, BIs may be helpful in reducing psychological distress. During this period, the available guidelines about AUDs may apply.

Breastfeeding is not recommended in the case of alcohol use or pharmacological treatment for maintenance of alcohol abstinence.

In some cases, alcohol use is associated with polyconsumption (including tobacco and illicit drugs), homelessness, comorbid psychiatric or somatic disorders, and domestic violence, which require specific psychosocial and/or medico-psychiatric care. The WHO published interesting recommendations for first-line intervention regarding the identification and management of intimate partner violence often associated to AUDs. Proper recording and referral should be encouraged (Clinical handbook at http://apps.who.int/iris/bitstream/10665/136101/1/WHO_RHR_14.26_eng.pdf), and clinical and policy guidelines (http://apps.who.int/iris/bitstream/10665/85249789241548595_eng.pdf).

Acknowledgements

The authors would like to thank Helen Hermann (WPA President) for her helpful comments and Pierre Mazeau for his help.

Statement of interest

F. Thibaut is Editor-in-Chief of *Dialogues in Clinical Neuroscience*. The journal receives a grant from Servier.

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