ALCOHOL CONSUMPTION DURING PREGNANCY: INTERVENTION GUIDANCE FOR THE PREVENTION OF FETAL ALCOHOL SPECTRUM DISORDERS

Daniela Fiorentino[1*], Valentina Carito[2], Simona Solombrino[1], Giovanna Coriale[1], Maria Concetta Marcella Scamporrino[1], Paola Ciolli[3], Marisa Patrizia Messina[3], Marco Fiore[2], Mauro Ceccanti[1]

[1]Latium Regional Center for Alcohol, "Sapienza" University of Rome,
[2]Institute of Cell Biology and Neurobiology, IBCN-CNR,
[3]Department of Gynecology-Obstetrics and Urological Science,
"Sapienza" University of Rome, Rome, Italy

ABSTRACT

Fetal Alcohol Spectrum Disorders (FASD) is a term used to describe the broad spectrum of pathologies and disorders caused by alcohol exposure in uterus. Since alcohol is able to directly cross the placental barrier, alcohol intake during pregnancy causes a broad range of symptoms whose severity can greatly vary in degree. It is already well established that Ethanol exhibits teratogenic effects resulting in growth delays, physical and specific facial anomalies, neurological defects including intellectual disabilities and behavioral problems. Since it is not possible yet to establish a safe threshold of consumption, the only feasible recommendation is the total abstention from alcohol during pregnancy. This work firstly presents an overview on FASD and reviews specific methodologies to overcome difficulties related to the investigation of alcohol behavior in pregnant women. Subsequently, different protocols of intervention are proposed according to different styles of alcohol consumption. The final goal is to provide clinicians with a range of methods in order to prevent damage to the newborns. Scr Sci Med. 2017;49(4):9-21

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Address for correspondence:
Daniela Fiorentino
Latium Regional Center for Alcohol,
"Sapienza" University of Rome
Via dell'Università, 37 00185, Rome
Italy
e-mail: danielafiorentino@yahoo.com

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INTRODUCTION

References to the effects of alcohol on newborns prenatally exposed to alcohol can be traced in ancient time in Aristotle and even in the Bible but was only in 1968 that they were described in a scientific paper titled "Anomalies in 121 children of alcoholics" by Lemoine *et al.* (1). Onward, Jones et al. (2,3) published several papers where a clear association between alcohol consumption in pregnancy and a specific syndrome in exposed newborns was de-

fined. Since then, over 3500 papers have been published in this issue (4) and nowadays alcohol is a very well-known and recognized teratogen for the fetus. Lifelong consequences of this pathology include brain damage and cognitive impairments with high costs for individuals and society (5,6). A review of the international guidelines on alcohol consumption during pregnancy shows that many countries all over the world officially released recommendations on the safest drinking behavior during pregnancy, from total abstention to no more than 1 or 2 drinks (standard drink=14 grams of alcohol; i.e. 330 ml of beer or 125 ml of wine) once or twice a week (i.e. United Kingdom - http://www.iard.org/Policy/Policy-Resources/Policy-Tables-by-Country/Drinking-Guidelines-for-Pregnancy-and-Breastfeeding). Some countries made health warning labels on alcoholic beverages mandatory: the US enacted such a law in 1989, China in 2005, France in 2006, Russian Federation and South Africa in 2007 (http://www.iard.org/Policy/Policy-Resources/Policy-Tables-by-Country/Health-Warning-Labeling-Requirements). But still, a percentage of women drinks during pregnancy and professionals in prenatal care suggest avoiding alcohol not as much as needed (7).

As the suspension of alcohol consumption during pre-conception time and pregnancy is able to prevent 100% of fetal alcohol effects, professionals' recommendations and early identification of at-risk women could be crucial.

FETAL ALCOHOL SPECTRUM DISORDERS (FASD)

Even if differences may exist in the main description of the syndrome, children prenatally exposed to alcohol share the following features: (*i*) specific facial anomalies, (*ii*) growth delay, and (*iii*) central nervous system (CNS) impairment, intellectual disabilities and behavioral problems.

The diagnosis of alcohol-related damages is mainly based on the use of four codes: the Institute of Medicine (IOM) criteria (8), the Canadian guidelines (9), the Four Digit Code (10) and the Center for Disease Control National Task force code (11). According to these codes the main altered facial features include: smooth philtrum, thin upper lip and short palpebral fissures; generally growth deficiencies are manifested in prenatal or postnatal birth weight or height below the tenth percentile, CNS dysfunctions include small head circumference (below the tenth percentile), brain structural anomalies, and a pervasive neurological deficit. Potentially, children affected may experience difficulties in memory, visual-spatial abilities, attention, logic and math abilities, verbal learning, information processing, executive functions as well as in other domains (12-15).

Fetal Alcohol Spectrum Disorders is a nondiagnostic term recently introduced (11, 16) to comprehend the whole range of possible alcohol-related damage in children exposed, including Fetal Alcohol Syndrome (FAS) or full syndrome, Partial FAS (PFAS), Alcohol-Related Birth Defects (ARBD), Alcohol-Related Neurodevelopmental Defects (ARND) (17). Alcohol consumption causes cognitive and behavioral impairments that affect individuals all their lifelong. Cognitive and behavioral main involved domains include global functioning, executive functioning, memory, visual-spatial ability, emotional functioning, motor functioning, attention and arousal levels, scholastic proficiency, verbal learning, language, mathematic, adaptive skills (18,19). As a consequence, individuals exposed may develop a number of secondary disabilities, including mental health problems (90%), low school proficiency and dropout (60%), trouble with the law (60%), inappropriate sexual behavior (49%), alcohol and drug problems (33%) (20). It should be noted that a complex interplay of genetic and epigenetic factors underlies the onset of FASD. Indeed, several studies have suggested a significant epigenetic FASD etiology and supporting evidence for such a mechanism is accumulating. Gene expression impairments can be caused by changes in DNA methylation, molecular modification of histones and through RNA interference. These mechanisms work together to elicit a unique, and reversible epigenetic signature regulating gene expression through chromatin remodelling. A mechanism of alcohol teratogenesis seems to be also DNA methylation (21,22).

FETAL ALCOHOL SPECTRUM DISORDERS PREVALENCE

Most of the prevalence studies, mainly registry or clinic-based, were performed in the United States. Registry-based studies consist in reviewing existing registries, including clinical records, disabilities registries and at birth diagnosis records (23). Thus far near-

ly 15 studies of this kind have been carried out, producing a mean FAS prevalence of 0.85 per 1,000 (median 0.27) while no data on FASD are provided (24).

Clinic studies consist in following women during pregnancy, collecting data on their alcohol consumption and then evaluating the newborns, very often in the form of prospective studies (24). More than 50 clinical studies reported in the literature indicates a mean prevalence rate of 1.8 for FAS (median – 1.9) and of 6 per 1000 for FASD (median – 5).

A minority of studies were conducted on non-clinical population, based on an active case ascertainment methodology, in which researchers actively evaluate a population in the field to individuate cases. These early studies have been carried out among native population in the US and Canada (25-27). This population, with low socio-economic status, may be considered at risk for alcohol consumption during gestation with elevated percentages of binge drinkers: therefore, the prevalence obtained was high and not easily generalizable. May (24) summarizes prevalence rates obtained from such a kind of studies: mean rate of FAS prevalence = 38.0 per 1000 (median = 9.0) and mean rate of FASD prevalence = 16.9 per 1000 (median = 19.0). A recent meta-analysis of active case ascertainment studies among children in child-care setting indicated a prevalence of 6.0% for FAS and 16.9% for FASD (28). The active case ascertainment method has been utilized also to highlight prevalence in the correctional system, leading to an estimate of the prevalence of 1.04% for FAS, 10% for PFAS and 4.1 to 8.7% for ARND (29). But in this case, as well results are not generalizable because of the at-risk condition of the selected settings.

This limit can be partially overcome by a particular kind of active strategy: the in-school active case ascertainment studies, where a general population of children attending school (usually 6-7 years old) is screened. The process of evaluation goes from the first screening for height, weight and head circumference, to an evaluation of behavioral problems and pre-learning skills, to the final dysmorphic exam and neuropsychological testing. An accurate interview of maternal drinking patterns and health conditions is performed as well (24). Most of these studies have been performed in South Africa: due to low socioeconomic conditions and high rates of alcohol consumption, they showed very high percentages of FASD occurrence (30-33). But recently active ascertainment in schools in the Western world revealed prevalence higher than what was expected. Table 1 resumes the prevalence rates found in in-school studies from around the world. Furthermore, a recent meta-analysis of in school studies (29), targeting general population of children enrolled in school and not including studies performed in South Africa, resumed prevalence rates as follows: FAS = 3.6 per 1000; PFAS 29 per 1000; ARND=2.3 per 1000 (Table 1).

Table 1. FAS/FASD rate per 1000 in different countries. Re-elaborated from (24)

Countries	FAS	FASD
	Rate per 1000	Rate per 1000
South Africa [30-33]	50.0	72.3
Washington, US [34]	3.1	
US [99]	4.3	
Italy, Europe [43-44]	4.0-8.2	23.1-47.1
US city 1 [24]	1.4-2.5	9.5-17.4
US city 2 [24]	6.4 -11.3	14.1-24.8
Plains Head Start School (US) [24]	10.2	20.3
Croatia, Europe [100]	6.4	40.7
Taiwan, [101]	1.83	5.76
Korea, General school, Institutions for intellectual disabilities [102]	2.8	14.9
Croatia, Europe rural [103]	16.9	66.7

RISK FACTORS

The full syndrome was estimated to occur in nearly 40% of heavily exposed pregnancies (34). The range and the severity of damage in children exposed are wide, depending on different variables, such as dose and timing of exposition, the nutritional status of the mother and genetic factors. An important risk factor for FASD is represented by the amount of alcohol consumed. Even if a safe threshold of consumption has not been established yet, an average consumption of more than 1 drink per day (14 grams of alcohol) may be considered at risk (35). However, a very high-risk behavior is represented by the exposure to great quantities in short time, since the damage on the fetus is directly related to the level of blood alcohol concentration (BAC) (31). This behavior is commonly referred to as "binge drinking", defined by the U.S. National Institute on Alcohol Abuse and Alcoholism (NIAAA) as the consumption causing a BAC level of 0.08 grams per liter or more. An adult woman reaches this level after the consumption of 4 or more drinks in two hours (36). Pointing at what can be considered a binge episode in pregnancy, a number of studies showed that the consumption of three or more drinks per single occasion is highly related to morphological and behavioral damage in exposed children (31).

Based on the well-demonstrated association between heavy episodic drinking or chronic drinking and negative outcomes in the offspring (37-40), research aiming at the evaluation of the effects of light consumption gave opposite results over the years, but evidence exists that even small amount of alcohol ingestion can affect the fetus, i.e. 0.5 alcohol units (nearly half of a standard drink) (41). The number of alcoholic beverages assumed is also correlated with heavier consumptions and could, therefore, be used as an indicator of at-risk drinking (42).

Epidemiological active-case ascertainment studies executed in Italy (43-45) demonstrated that in a retrospective interview, mothers of FASD children consumed a higher number of drinks per week, at current, compared to controls (FASD Mean=10.37, standard deviation 18.92; Controls, Mean=1.52, standard deviation=2.80, $p<0.001$). It was suggested that current drinking could represent a more reliable measure of drinking because less susceptible to social stigma. Similar effects can be observed for self-report of drinking out of pregnancy.

Another aspect that should be taken into consideration is the kind of alcoholic beverage consumed. Studies on animal models (46-49) investigated damage differences due to gestational exposure to wine versus other alcoholic beverage, comparing mice prenatally exposed to 11% ethanol or to the same concentration of red wine. Data showed that administration in utero of ethanol-induced long-lasting changes in offspring behavior, brain areas, endocrine tissues and liver, while in mice exposed to red wine the peripheral tissues but not brain structures were affected. These differences in toxicity could be explained by the presence in red wine of polyphenol compounds showing neuroprotective and antioxidant effects (50-54). Moreover, mother's age, nutritional status, body size, parity, socioeconomic status and other drugs use, as well as genetic and epigenetic factors, are other factors affecting the offspring (55-58).

Animal model and human studies showed that paternal alcohol exposure (PAE) only may also elicit changes in the newborns comparable to those observed with gestational ethanol exposure (59-61). Indeed, contrary to the large attention given to the roles that maternal factors have on the outcome of pregnancy, little is currently known about the possible function played by paternal factors, especially about the influence of PAE on the developmental and neurobehavioral characteristics of offspring (68). It has been suggested that about 75 percent of children affected by FAS have heavy drinkers or alcoholic biological fathers (61). These findings indicate that the anomalies in the newborns attributed to the influence of the teratogenic effects of maternal drinking are also the consequence of the PAE, suggesting that the anomalies could be due to or are exacerbated by paternal drinking. The occurring of alcohol problems in the family environment also should be taken into consideration as a risk factor. As was shown in an Italian active case ascertainment study (45) the occurrence of alcohol problems in the child's family was the most significant risk factor for FASD. Furthermore, sequential multiple regression analysis of the neuropsychological performance of tested children identified the occurrence of alcohol problems in mothers' family as the only significant risk variable related to mothers.

ALCOHOLIC ANAMNESIS AND DETECTION OF AT-RISK WOMEN

A recent meta-analysis by Popova *et al.* (62) describes prevalence estimates of alcohol consumption in pregnancy throughout the World in general population: world-wide prevalence was 9.8%, the highest prevalence was found in Europe (25.2%), the lowest in Eastern Mediterranean Region (0.2%) and the prevalence in the Region of the Americas was 11.2%.

In Italy, a multicenter analysis found different levels of fetal exposure to ethanol in different cities (0% to 29.4%) through the objective measurement of meconium biomarkers (63). In a Spanish study, the 45% of the meconium samples exceeded the cut-off limit (>2 nmol/g) (64). These data indicate that gestational ethanol exposure is widespread, at least in parts of Europe. Thus, the identification of women still drinking during pregnancy has main implications for prevention.

Inaccurate self-reports of drinking very often derive from the perception of social stigma especially as regards alcohol consumption during pregnancy. Embarrassment in giving honest answers determines underestimation of the personal consumption (65). Several instruments can be used to gather realistic information about alcohol consumption. One of this is the quantity/frequency/variability method that evaluates mean amounts consumed per day, their frequency and whether peaks of consumption occur (66). According to this method, questions may be: on a typical day when you drink, how many drinks do you have? On average, how many days per week do you drink alcohol? What is the maximum number of drinks you had on any given occasion during the last month?

The Timeline Follow-Back is another commonly used method (67), where questions are made anchoring them to important events in the past such as holidays and parties, to facilitate recollection of personal drinking behavior. Questions can be asked also referring to the last week. This method may increase the chances of a more accurate personal consumption recalling but it lacks to evaluate consumption in less regular drinkers, especially during pregnancy (68).

In general, to avoid social stigma it is recommended to imbibe questions about drinking in the context of a diet diary (69). Moreover, people usually can not exactly evaluate amounts of their drinking due to the several different sizes of existing glasses. A visual aid, such as pictures depicting standard drinks and glass sizes of different kind of alcoholic beverages, can be showed in order to correctly identifying quantities (70) so that women can understand the exact meaning of the word "drink", when asked about their alcohol consumption.

Many screening tests have been developed to identify at-risk consumption in the general population but they often fail when used to identify pregnant women drinking (71) because they target men's patterns of consumption more than women and because they are aimed at identifying addiction, that is not a very common situation in prenatal care. However, specific screening instruments for pregnant women have been developed. A review (72) compared 7 different screening tests and 3 of them showed more sensitivity and higher specificity: the TWEAK (73), the AUDIT-C (74) and the T-ACE (75) (Table 2). In particular, the AUDIT-C showed the highest sensitivity in identifying pathologic abuse. Chang (71) compared the T-ACE with three widely used screening tests: the AUDIT (76), the SMAST (77) and medical records of patients. The T-ACE resulted the most sensitive in the detection of current alcohol consumption, risky drinking, and diagnoses of alcohol problems according to DSM-III-R during a lifetime. A recent study, however, found a marked underestimation of gestational alcohol consumption if measured with 4 alcohol screening questionnaires (TWEAK, AUDIT-C, T-ACE, food diary) and compared with ethyl glucoronide in the urine of the pregnant women, a direct biomarker of ethanol consumption (78).

Pregnant women drinking alcohol and children exposed can also be identified by the use of other biomarkers, as fatty acid ethyl esters (FAEEs) traced in the meconium. These markers of alcohol consumption can be measured during the second and the third trimester of pregnancy, as this non-oxidative metabolite accumulates in the meconium when alcohol is metabolized (79). As already mentioned, in Spain, the 45% of the meconium samples exceeded the cut-off limit (>2 nmol/g) (64) while in the above mentioned Italian multicentric study different rates of alcohol exposition were found, ranging from 0% to 29.4% (65). This method, even if it does not allow prenatal identification, could be considered useful to

identify high-risk children. To overcome this limitation, FAEEs can be traced also in maternal hair (80). At present, other biomarkers are studied such as micro-RNA and potential proteomic and metabolic markers (81) (see Table 2).

and Gynecologists and the American Academy of Pediatrics as well as the US Office of the Surgeon General and the US Department of Health and Human Services, support prevention strategies that recognize the pivotal role of the health care providers in

Table 2. TWEAK, AUDIT-C and T-ACE description

TWEAK [73] **T** Tolerance: How many drinks can you hold? (Score 2 points for more than 2 drinks; Score 0 for 2 drinks or less) **W** Have close friends or relatives Worried or complained about your drinking in the past year? Score 2 point if Yes **E** Eye Opener: Do you sometimes take a drink in the morning when you get up? Score 1 point if Yes **A** Amnesia: Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember? Score 1 point if Yes **K(C)** Do you sometimes feel the need to Cut down on your drinking? Score 1 point if Yes **Total score of 2 or more indicates at risk drinking**
AUDIT-C [74] How often do you have a drink containing alcohol? Never (0) Monthly or less (1) Two to four times a month (2) Two to three times a week (3) Four or more times a week (4) How many units of alcohol do you drink on a typical day when you are drinking? None, I do not drink (0) 1 or 2 (0) 3 or 4 (1) 5 or 6 (2) 7 to 9 (3) 10 or more (4) How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year? Never (0) Less than monthly (1) Monthly (2) Weekly (3) Daily or almost daily (4) **In men a total score of 4 or more indicates at risk drinking** **In women a total score of 3 or more indicates at risk drinking**
T-ACE [75] **T** Tolerance: How many drinks does it take to make you feel high? (Score 2 points for more than 2 drinks; Score 0 for 2 drinks or less) **A** Have people Annoyed you by criticizing your drinking? Score 1 point if Yes **C** Have you ever felt you ought to Cut down on your drinking? Score 1 point if Yes **E** Eye opener: Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? Score 1 point if Yes **Total score of 2 or more indicates at risk drinking**

INTERVENTION PROTOCOLS

Total abstention from drinking during pregnancy seems to be the best practice, according to official statements by governmental agencies and medical boards. The American College of Obstetricians

informing, counselling and referring women at risk for an alcohol-exposed pregnancy (82).

In order to target women of childbearing age, prevention efforts should start before pre-concep-

tional period. All childbearing-aged women should be screened for alcohol use, as recommended by the Clinical Working Group of the Select Panel on Preconception Care from American Center for Disease Control and Prevention (CDC) in 2008 (83) and WHO's Guidelines for the identification and management of substance use and substance use disorders in pregnancy (84). A recent review of 29 studies aimed at testing a preventive intervention targeting pregnant and non-pregnant women shows promising results of preventive efforts, even if not conclusive yet (85).

Undergoing a screening for alcohol consumption can itself induce a reduction in alcohol use (86). Giving information on the consequences of alcohol use during pregnancy is also strongly recommended by CDC. It can be speculated that pregnant women previously informed about the risks related to alcohol exposure in pregnancy could drink less or quit drinking during gestation than those not correctly advised about prenatal alcohol consumption. Indeed, good results were obtained with women who had been exposed to preventive leaflets compared to those not exposed (42). Pregnancy, in fact, is believed to be a moment in which women are very motivated to protect baby's and their own health (87). However, in heavier drinkers, the information on alcohol-related consequences alone may not be effective. Handmaker *et al.* (88) demonstrated that mailing a letter or delivering a motivational session were both effective in reducing alcohol use in a group of pregnant women, while only the motivational session was effective in reducing consumption in heavy drinkers. Similar results were obtained by Chang *et al.* (89), Tzlos *et al.* (90) and Osterman *et al.* (91).

Motivational sessions (92) and brief interventions (92-93) have proved to be effective in reducing alcohol use in pregnant women. These techniques can be used by professionals not specialized in alcohol abuse treatment and are low-cost not time-consuming interventions (82). The Acronym FRAMES is used to resume key elements in effective interventions: feedback on personal risk; advise for a change; a menu of strategies to cut on drinking; personal responsibility, empathic communication style; focus on self-efficacy (94).

Women consuming both alcohol and drugs and those who have already delivered a FASD child are the most at-risk women. Chances to have another affected child may be as high as 75% (95-96). Treatment of these cases is complex and includes intensive case management and deep collaboration among several agencies and health services. Also, women abusing alcohol need effective contraceptive counselling and should be referred to an addiction treatment program in specialized units (11, 82). Based on these considerations, to prevent alcohol-exposed pregnancies, standardized protocols of intervention are required (97). First, universal preventive actions to prevent alcohol-exposed pregnancies targeting all the women of childbearing age have to be undertaken: questions inquiring alcohol drinking should be routinely included in patient's anamnesis. Alcohol anamnesis should be performed in the context of a general investigation into eating habits. All the women, drinking or not, should be informed about consequences of alcohol consumption in pregnancy and, in case, be suggested to suspend consumption if planning a pregnancy. Second, when targeting pregnant women, detection of alcohol use and screening tests are needed. In the context of alcohol anamnesis, questions about alcohol habits before pregnancies should be asked as well, in order to identify heavy drinkers. The above mentioned AUDIT-C questionnaire can be used to investigate before pregnancy alcohol consumption and identify heavy drinkers. Also, questions about the occurring of alcohol abuse in partner or family can be useful to inform the clinician if the woman lives in an at-risk environment. After the alcohol anamnesis, pregnant patients can be grouped into four categories, each requiring specific interventions.

1. Not at-risk women: women who do not drink during pregnancy. It can be useful reaffirming the importance of total abstention to reinforce behavior and to have women spreading the health message in their personal environment.
2. Mild risk women: pregnant women drinking alcohol occasionally or less than one drink per day and not binging. As a safe threshold has not been established yet, all women consuming alcohol in pregnancy are considered potentially at risk and should be informed about the risks for the babies; total abstention from alcohol must be recommended. In this case, a single brief counselling session could be enough to ensure a safe pregnancy.

3. At-risk women: pregnant women, presenting one or more among risk factors. The following risk factors could be considered: consumption of more than one drink per day or three or more in a single occasion; variety of beverages consumed; positive answer to the T-ACE question about tolerance (two drinks or more needed to experience some alcohol effects), presence of heavy drinking before pregnancy (e. g. ascertained through the AUDIT-C), partner's problematic alcohol consumption and alcohol problems in family environment. These women may need more structured counselling sessions or sessions following the FRAMES model cited above, to enhance chances of a behavioral change.
4. High-risk women: when there is clear evidence of abuse and addiction or a patient has already had a heavy alcohol-exposed pregnancy or has already delivered an affected child, it is strongly recommended to refer the patient to a proper alcohol treatment unit, and work together to maximize chances of a safe pregnancy.

Early detection of alcohol consumption during pregnancy is essential both for its preventive and therapeutic implications. While a simple suggestion by professionals' can persuade mild drinkers to give up consumption, when damage has not occurred yet, the knowledge that a pregnancy is at risk for alcohol drinking allows particular interventions also through nutritional supplementation. Indeed, optimal maternal nutritional status is of utmost value for proper fetal development frequently altered with alcohol exposure. Several investigations in animal models and humans addressed the role of prenatal nutrition as possible interventions for FASD throughout several nutrients supplementation (vitamin A, docosahexaenoic acid, folic acid, zinc, choline, vitamin E, and selenium) that may prevent or counteract the development of FASD (reviewed in 98).

CONCLUSION

The burden of lifelong disabilities caused by alcohol consumption during pregnancy is extreme at individual, familial and societal level. In recent years the implementation of active case ascertainment methods for establishing prevalence in general population revealed higher rates than those estimated through passive surveillance methods or clinic studies. Public agencies all over the world underline the crucial importance of the enactment of laws on labelling alcoholic beverages and the release of health statements recommending total abstinence from alcohol during pregnancy as an important way of prevention. As far as a safe consumption behavior can not be established, for the extremely individual conditions of susceptibility to alcohol, risk factors should be screened and addressed in women at child bearing age. Obstetrics and gynaecologists are in the first line to face the issue and can do a lot in preventing FASD by routinely performing an alcohol anamnesis during prenatal care and before it. Gaining a realistic estimation of patient's alcohol intake is possible if validated instruments and methods are adopted. Professionals dealing with women health can be trained to perform accurate alcohol anamnesis, screening and brief counselling interventions. Fostering these skills will permit them to adopt protocols matching risky conditions with proper interventions to maximize the possibility of a healthy pregnancy.

Authors Disclosure Statement

All the authors state that no competing financial interests exist.

REFERENCES

1. Lemoine P, Harousseau H, Borteyru JP. Menuet JC. Les enfants des parents alcoholiques: anomolies observées a propos de 127 cas. Ouest Med 1968; 8: 476-82.
2. Jones KL, Smith DW, Ulleland CN Streissguth P. Pattern of malformation in offspring of chronic alcoholic mothers. Lancet 1973; 1: 1267-71. DOI:10.1016/S0140-6736(73)91291-9
3. Jones K, Smith D. Recognition of the fetal alcohol syndrome in early infancy. Lancet 1973; 2: 999-1001. DOI:10.1016/S0140-6736(73)91092-1
4. Riley EP, Infante MA, Warren KR. Fetal alcohol spectrum disorders: An overview. Neuropsychol Rev 2011; 21: 73-80. DOI: 10.1007/s11065-011-9166-x
5. Lupton C, Burd L, Harwood R. Cost of fetal alcohol spectrum disorders. Am J Med Genet C Semin Med Gene 2004; 15;127C:42-50. DOI: 10.1002/ajmg.c.30015
6. Popova S, Lange S, Bekmuradov D, Mihic A. Fetal Alcohol Spectrum Disorder prevalence estimates in correctional systems: a systematic literature

review. Can J Public Health 2011; 102:336-40. PMID:22032097

7. Vagnarelli F, Palmi I, Garcia-Algar O, Falcon M, Memo L, Tarani L, Spoletini R, Pacifici R, Mortali C, Pierantozzi A, Pichini S. A survey of Italian and Spanish neonatologists and paediatricians regarding awareness of the diagnosis of FAS and FASD and maternal ethanol use during pregnancy. BMC Pediatrics 2011;11:51. DOI:10.1186/1471-2431-11-51

8. Hoyme HE, Kalberg WO, Elliott AJ, Blankenship J, Buckley D, Marais AS, et al. Updated clinical guidelines for diagnosing Fetal Alcohol Spectrum Disorders, Pediatrics 2016;138:1-18. DOI:10.1542/peds.2015-4256

9. Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. Can Med Assoc J 2005; 172(Suppl 5):S1-S21. DOI:10.1503/cmaj.1040302

10. Astley SJ, Clarren SK. Diagnosing the full spectrum of fetal alcohol-exposed individuals: introducing the 4-digit diagnostic code. Alcohol Alcoholism 2000;35:400-10.

11. Bertrand J, Floyd LL, Weber MK. Guidelines for identifying and referring persons with fetal alcohol syndrome. MMWR Recomm Rep. 2005;54(RR-11):1-14. https://www.cdc.gov/mmwr/PDF/rr/rr5411.pdf

12. Mattson SN, Riley EP, Delis DC, Stern C, Jones KL. Verbal learning and memory in children with fetal alcohol syndrome. Alcohol Clin Exp Res 1996;20:810-6. DOI:10.1111/j.1530-0277.1996.tb05256.x

13. Kodituwakku PW, Handmaker NS, Cutler SK, Weathersby E, Handmaker SD. Specific impairments in self-regulation in ildren exposed to alcohol prenatally. Alcohol Clin Exp Res 1995;19:1558-64. DOI: 10.1111/j.1530-0277.1995.tb01024.x

14. Olson HC, Feldman JJ, Streissguth AP, Sampson PD, Bookstein FL, Neuropsychological deficits in children with fetal alcohol syndrome: Clinical findings. Alcohol Clin Exp Res 1998;22:1998-2012. DOI: 10.1111/j.1530-0277.1998.tb05909.x

15. Sokol RJ, Delaney-Black V, Nordstrom B. Fetal alcohol spectrum disorder. J Am Med Assoc. 2003;290:2996-9. DOI:10.1001/jama.290.22.2996

16. Coriale G, Fiorentino D, Di Lauro F, Marchitelli R, Scalese B, Fiore M, Maviglia M, Ceccanti M. Fetal Alcohol Spectrum Disorder (FASD): neurobehavioral profile, indications for diagnosis and treatment. Riv Psichiatr 2013;48: 359-69. DOI: 10.1708/1356.15062

17. Kline J, Shrout P, Stein Z, Susser M, Warburton D. Drinking during pregnancy and spontaneous abortion. Lancet 1980;2(8187):176–180. DOI:10.1016/S0140-6736(80)90062-8

18. Mattson SN, Riley EP. A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. Alcohol Clin Exp Res 1998;22:279-94. DOI: 10.1111/j.1530-0277.1998.tb03651.x

19. Kodituwakku PW, Kodituwakku EL. From research to practice: An integrative framework for the development of interventions for children with fetal alcohol spectrum disorders. Neuropsychol Rev 2011;21:204-23. DOI: 10.1007/s11065-011-9170-1

20. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr 2004;25:228-38.

21. Mead EA, Sarkar DK. Fetal alcohol spectrum disorders and their transmission though genetic and epigenetic mechanism. Front Genet 2014; 5:154. DOI: 10.3389/fgene.2014.00154

22. Resendiz M, Mason S, Lo CL, Zou FC Epigenetic regulation of the neural transcriptome and alcohol interference during development. Front Genet 2014;26;5:285. DOI: 10.3389/fgene.2014.00285.

23. May PA, Gossage JP, Kalberg WO, Robinson LK, Buckley D, Manning M, et al. Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. Dev Disabil Res Rev 2009;15:176-92. DOI: 10.1002/ddrr.68

24. May PA. Researching the prevalence and characteristics of FASD in international settings. In: Riley EP, Clarren S, Weinberg J, Jonsson E, eds. Fetal Alcohol Spectrum Disorder: Management and Policy Perspectives of FASD. Hoboken NJ: Wiley Blackwell, 2010: 15-25. DOI:10.1002/9783527632510.ch2

25. May PA, Hymbaugh KJ. A pilot project on fetal alcohol syndrome among American Indians. Alcohol Health Res 1982;7:3-9.

26. May PA, Hymbaugh KJ, Aase JM, Samet JM. Epidemiology of fetal alcohol syndrome among American Indians of the Southwest. Soc Biol 1983;30:374-85.

27. May PA, McCloskey J, Gossage JP. Fetal alcohol syndrome among American Indians: epidemiology, issues, and research review. In: Mail PD, Heurtin-Roberts S, Martin SE, Howard J, eds. Alcohol use among American Indians and Alaska Natives: multiple perspectives on a complex problem. Vol. 13. Bethesda, MD: US Dept. of Health and Human Services. NIAAA 2002. Monograph no. 37. 321-369.

28. Lange S, Shield K, Rehm J, Popova S. Prevalence of Fetal Alcohol Spectrum Disorders in child Care settings: a meta-analysis. Pediatrics 2013;132:980-95. DOI: 10.1542/peds.2013-0066.

29. Ospina M, Dennett L. Systematic review on the prevalence of Fetal Alcohol Spectrum Disorders. IHE Institute of Health Economics, Alberta, Canada; April 2013.

30. May PA, Brooke LE, Gossage JP, Croxford J, Adnams C, Jones KL, et al. Epidemiology of fetal alcohol syndrome in a South African Community in the Western Cape Province. Am J Public Health 2000;90:1905-12. http://ajph.aphapublications.org/doi/10.2105/AJPH.90.12.1905

31. Viljoen DL, Gossage JP, Brooke L, Adnams, CM, Jones KL, Robinson LK, et al. Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. J Stud Alcohol 2005;66:593-604. https://doi.org/10.15288/jsa.2005.66.593

32. May PA, Gossage JP, Marais AS, Adnams CM, Hoyme HE, Jones KL, et al. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend 2007;88:259-71. DOI: 10.1016/j.drugalcdep.2006.11.007

33. May PA, Blankenship J, Marais AS, Gossage JP, Kalberg WO, Joubert B, et al. Maternal alcohol consumption producing fetal alcohol spectrum disorders (FASD): quantity, frequency, and timing of drinking. Drug Alcohol Depend 2013;133(2):502-12 DOI: 10.1016/j.drugalcdep.2013.07.013

34. Stratton K, Howe C, Battaglia F. Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment. National Academy Press: Washington, DC, USA; 1996.

35. Hankin JR, Sokol RJ. Identification and care of problems associated with alcohol ingestion in pregnancy. Semin Perinatol 1995;19:286-292.

36. NIAAA, National Institute of Alcohol Abuse and Alcoholism Council approves definition of binge drinking. 2004; NIAAA Newsletter No 3 Winter.

37. Bonati M, Fellin G. Changes in smoking and drinking behaviour before and during pregnancy in Italian mothers: implications for public health intervention. Int J Epidemiol 1991;20:927–932.

38. NIAAA (National Institute on Alcohol Abuse and Alcoholism). Eighth special report to the U.S. Congress on alcohol and health from the Secretary of Health and Human Services. Washington, DC: U.S. Government Printing Office, 1993.

39. IOM (Institute of Medicine). Fetal alcohol syndrome: Diagnosis, epidemiology, prevention, and treatment. Washington, DC: The National Academy Press; 1996.

40. Plant ML, Abel EL, Guerri C. Alcohol and pregnancy. In I. Macdonald eds. Health issues related to alcohol consumption 2nd ed. Oxford, UK: Blackwell Science, 1999, 182-213.

41. Sood B, Delaney-Black V, Covington C, Nordstrom-Klee B, Ager J, Templin T, et al. Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect. Pediatrics 2001;108:E34. doi: 10.1542/peds.108.2.e34

42. Ceccanti M, Fiorentino F, Vitali M. Facing Fetal Alcohol Spectrum Disorders in Italy. Fetal Alcohol Forum. 2015;11:37-42. Available at http://www.no-fas-uk.org/?cat=29.

43. May PA, Fiorentino D, Gossage PJ, Kalberg WO, Hoyme EH, Robinson LK, et al. Epidemiology of FASD in a province in Italy: Prevalence and characteristics of children in a random sample of schools. Alcohol Clin Exp Res 2006;30(9):1562-75. DOI: 10.1111/j.1530-0277.2006.00188.x

44. May PA, Fiorentino D, Coriale G, Kalberg WO, Hoyme HE, Aragon AS, et al. Prevalence of children with severe fetal alcohol spectrum disorders in communities near Rome, Italy: New estimated rates are higher than previous estimates. Int J Environ Res Public Health 2011;8:2331-51. DOI: 10.3390/ijerph8062331

45. Ceccanti M, Fiorentino D, Coriale G, Kalberg WO, Buckley D, Hoyme HE, et al. Maternal risk factors for fetal alcohol spectrum disorders in a province in Italy. Drug Alcohol Depend 2014;145:201-8. DOI: 10.1016/j.drugalcdep.2014.10.017

46. Fiore M, Laviola G, Aloe L, Di Fausto V, Mancinelli R, Ceccanti M. Early exposure to ethanol but

not red wine at the same alcohol concentration induces behavioral and brain neurotrophin alterations in young and adult mice. Neurotoxicology 2009;30:59-71. DOI: 10.1016/j.neuro.2008.11.009

47. Fiore M, Mancinelli R, Aloe L, Laviola G, Sornelli F, Vitali M, Ceccanti M. Hepatocyte growth factor, vascular endothelial growth factor, glial cell-derived neurotrophic factor and nerve growth factor are differentially affected by early chronic ethanol or red wine intake. Toxicol Lett 2009;188:208-13. DOI: 10.1016/j.toxlet.2009.04.013

48. Ceccanti M, Mancinelli R, Tirassa P, Laviola G, Rossi S, Romeo M, Fiore M. Early exposure to ethanol or red wine and long-lasting effects in aged mice. A study on nerve growth factor, brain-derived neurotrophic factor, hepatocyte growth factor, and vascular endothelial growth factor. Neurobiol Aging 2012;33:359-67. DOI: 10.1016/j.neurobiolaging.2010.03.005

49. Ceccanti M, De Nicolò S, Mancinelli R, Chaldakov G, Carito V, Ceccanti M, et al. NGF and BDNF long-term variations in the thyroid, testis and adrenal glands of a mouse model of fetal alcohol spectrum disorders. Ann Ist Super Sanita 2013;49:383-90. DOI: 10.4415/ANN_13_04_11

50. De Nicolo' S, Tarani L, Ceccanti M, Maldini M, Vania A, Chaldakov GN, Fiore M. Effects of olive polyphenols administration on nerve growth factor and brain derived neurotrophic factor in the mouse brain. Nutrition 2013;29:681-7. DOI 10.1016/j.nut.2012.11.007.

51. Ceccanti M, Carito V, Iannuzzi S, Vitali M, Tarani L, De Nicolo S, et al. Serum BDNF and NGF modulation by olive polyphenols in alcoholics during withdrawal. J Alcohol Drug Depend 2015;3:214. DOI:10.4172/23296488.1000214

52. Carito V, Ciafre S, Tarani L, Ceccanti M, Natella F, Iannitelli A, et al. TNF-alpha and IL-10 modulation induced by polyphenols extracted by olive pomace in a mouse model of paw inflammation. Ann Istit Super Sanita 2015, 51, 382-6. DOI: 10.4415/ANN_15_04_21

53. Carito V, Ceccanti M, Tarani L, Ferraguri G, Chaldakov GN, Fiore M. Neurotrophins' modulation by olive polyphenols. Curr Med Chem 2016, 23: 3189-3197. DOI: 10.2174/0929867323666160627104022

54. Carito V, Ceccanti M, Cestari V, Natella F, Bello C, Coccurello R, et al. Olive polyphenols effects in a mouse model of chronic ethanol addiction. Nutrition 2017, 33: 65-9. DOI:10.1016/j.nut.2016.08.014

55. Jacobson JL, Jacobson SW, Sokol RJ, Martier SS, Ager JW, Kaplan-Estrin MG Teratogenic effects of alcohol on infant development. Alcohol Clin Exp Res 1993;17:174–183. DOI: 10.1111/j.1530-0277.1993.tb00744.x

56. Abel EL, Hannigan JH. Maternal risk factors in fetal alcohol syndrome: provocative and permissive influences. Neurotoxicol Teratol 1995;17:445–62. https://doi.org/10.1016/0892-0362(95)98055-6

57. Ebrahim SH, Diekman ST, Floyd RL, Decoufle P. Comparison of binge drinking among pregnant andnonpregnant women, United States, 1991-1995. Am J Obstet Gynecol 1999;180:1-7. DOI:10.1016/S0002-9378(99)70139-0

58. Roberts G, Nanson J. Best practices: fetal alcohol syndrome/fetal alcohol effects and the effects of other substance use during pregnancy. Canada's Drug Strategy Division, Health Canada 2000.

59. Abel EL. Paternal and maternal alcohol consumption: effects on offspring in two strains of rats. Alcohol Clin Exp Res 1989;13:533-41.

60. Abel E. Paternal contribution to fetal alcohol syndrome. Addict Biol 2004;9:127-33. DOI: 10.1111/j.1530-0277.1989.tb00373.x

61. Ceccanti M, Coccurello R, Carito V, Ciafrè S, Ferraguti G, Giacovazzo G, et al. Paternal alcohol exposure in mice alters brain NGF and BDNF and increases ethanol-elicited preference in male offspring. Addict Biol 2016; 21, 779-87. DOI: 10.1111/adb.12255

62. Popova S, Lange S Probst C, Gmel G, Rehm J. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta analysis. Lancet Glob Health. 2017;5:e290-e299 DOI: 10.1016/S2214-109X(17)30021-9

63. Pichini S, Marchei E, Vagnarelli F, Tarani L, Raimondi F, Maffucci R, et al. Assessment of prenatal exposure to ethanol by meconium analysis: results of an Italian multicenter study. Alcohol Clin Exp Res 2012;36:417-24. DOI: 10.1111/j.1530-0277.2011.01647.x

64. Garcia-Algar O, Kulaga V, Gareri J, Koren G, Vall O, Zuccaro P, et al. Alarming prevalence of fetal alcohol exposure in a Mediterranean city. Ther Drug Monit 2008;30:249-54. DOI: 10.1097/FTD.0b013e31816a8657

65. Morrow-Tlucak M, Ernhart CB, Sokol RJ, Martier S, Ager J. Underreporting of alcohol use in preg-

nancy: relationship to alcohol problem history. Alcohol Clin Exp Res 1989; 13(3):399–401. DOI: 10.1111/j.1530-0277.1989.tb00343.x

66. Allen JP, Columbus M. Assessing Alcohol Problems: A Guide for Clinicians and Researchers. National Institute on Alcohol Abuse and Alcoholism Treatment Handbook Series 4. NIH Pub. No. 95–3745. Bethesda, MD: the Institute, 1995.

67. Sobell LC, Sobell MB. Timeline follow-back: A technique for assessing self-reported alcohol consumption. In: R.Z. Litten, J. Allen, eds. Measuring alcohol consumption: Psychosocial and biological methods. New Jersey: Humana Press, 1992; 41-72.

68. Bloomfield K, Hope A, Kraus L. Alcohol survey measures for Europe: A literature review. Drugs Educ Prev Policy 2013;20:348-60. DOI10.3109/09687637.2011.642906

69. King AC. Enhancing the self-report of alcohol consumption in the community: two questionnaire formats. Am J Public Health 1994;84:294-6. http://ajph.aphapublications.org/doi/10.2105/AJPH.84.2.294

70. Kerr WC, Stockwell T. Understanding standard drinks and drinking guidelines. Drug Alcohol Rev 2012;31:200-5. DOI: 10.1111/j.1465-3362.2011.00374.x

71. Chang G. Alcohol-screening instruments for pregnant women. Alcohol Res Health 2001;25:204-9. https://pubs.niaaa.nih.gov/publications/arh25-3/204-209.htm

72. Burns E, Gray R, Smith LA. Brief screening questionnaires to identify problem drinking during pregnancy: a systematic review. Addiction 2010;105(4):601–614. DOI: 10.1111/j.1360-0443.2009.02842.x

73. Chan AW, Pristach EA, Welte JW, Russell M. Use of the TWEAK test in screening for alcoholism/heavy drinking in three populations. Alcohol Clin Exp Res 1993;17:1188-92. DOI: 10.1111/j.1530-0277.1993.tb05226.x

74. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med 1998;158:1789-95. doi:10.1001/archinte.158.16.1789

75. Sokol RJ, Martier SS, Ager JW. The T-ACE questions: practical prenatal detection of risk-drinking. Am J Obstet Gynecol 1989;160:863-8. https://doi.org/10.1016/0002-9378(89)90302-5

76. Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with armful alcohol consumption – II. Addiction 1993;88:791-803. DOI: 10.1111/j.1360-0443.1993.tb02093.x

77. Selzer ML, Vinokur A, Van Rooijen L. A self-administered Short Michigan Alcoholism Screening Test (SMAST). J Stud Alcohol 1975;36:117-26. https://doi.org/10.15288/jsa.1975.36.117

78. Ferraguti G, Ciolli P, Carito V, Battagliese G, Mancinelli R, Ciafrè S, et al. Ethylglucuronide in the urine as a marker of alcohol consumption during pregnancy: comparison with four alcohol screening questionnaires. Toxicol Lett 2017, 275, 49-56. DOI: 10.1016/j.toxlet.2017.04.016

79. Lange S, Shield K, Koren G, Rehm J, Popova S. A comparison of the prevalence of prenatal alcohol exposure obtained via maternal self-reports versus meconium testing: a systematic literature review and meta-analysis. BMC Pregnancy Childbirth 2014;14:127. DOI: 10.1186/1471-2393-14-127

80. Kulaga V, Shor S, Koren G. Correlation between drugs of abuse and alcohol by hair analysis: parents at risk for having children with fetal alcohol spectrum disorder. Alcohol 2010; 44:615–21. DOI: 10.1016/j.alcohol.2010.04.001

81. Datta S, Turner D, Singh R, Ruest LB, Pierce WM Jr, Knudsen TB. Fetal alcohol syndrome (FAS) in C57BL/6 mice detected through proteomics screening of the amniotic fluid. Birth Defects Res A Clin Mol Teratol 2008;82:177–86. DOI: 10.1002/bdra.20440

82. Floyd RL, Ebrahim S, Tsai J, O'Connor M, Sokol R. Strategies to reduce alcohol-exposed pregnancies. Matern Child Health J 2006;10(5 Suppl):S149–151. DOI: 10.1007/s10995-006-0116-9

83. Floyd RL, Jack BW, Cefalo R, Atrash H, Mahoney J, Herron A, et al. The clinical content of preconception care: alcohol, tobacco and illicit drug exposures. Am J Obstet Gynecol 2008;199:S333-S339. DOI: 10.1016/j.ajog.2008.09.018

84. WHO Guidelines for the identification and management of substance use and substance use disorders in pregnancy. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstre

am/10665/107130/1/9789241548731_eng.pdf?ua=1, accessed 9 July 2016)

85. Schölin L. Prevention of harm caused by alcohol exposure in pregnancy. Rapid review and case studies from Member States, WHO, 2016. http://www.euro.who.int/data/assets/ pdf_ file/0005/318074/Prevention-harm-caused-alcohol-exposure-pregnancy.pdf

86. Chang G. Screening for alcohol and drug use during pregnancy. Obstet Gyn Clin North Am 2014;41:205-12. DOI: 10.1016/j.ogc.2014.02.002

87. Higgins PG, Clough DH, Frank B, Wallerstedt C. Changes in health behaviors made by pregnant substance users. Int J Addict 1995;30:1323–1333.

88. Handmaker NS, Miller WR, Manicke M. Finding of a pilot study of motivational interviewing with pregnant drinkers. J Stud Alcohol 1999; 60:285–287. https://doi.org/10.15288/jsa.1999.60.285

89. Chang G, McNamara TK, Orav EJ, Koby D, Lavigne A, Ludman B, et al. Brief intervention for prenatal alcohol use: a randomized trial. Obstet Gynecol. 2005;105 (5 Pt 1):991–8. DOI: 10.1097/01.AOG.0000157109.05453.84

90. Tzilos GK, Sokol RJ, Ondersma SJ. A randomized phase I trial of a brief computer-delivered intervention for alcohol use during pregnancy. J Womens Health. 2011;20:1517–24. DOI: 10.1089/jwh.2011.2732

91. Osterman RL, Carle AC, Ammerman RT, Gates D. Single-session motivational intervention to decrease alcohol use during pregnancy. J Subst Abuse Treat.2014;47:10–9. DOI: 10.1016/j.jsat.2014.01.009

92. Floyd RL, Sobell M, Velasquez MM, Ingersoll K, Nettleman M, Sobell L, et al. Project CHOICES Efficacy Study Group. Preventing alcohol-exposed pregnancies: a randomized controlled trial. Am J Prev Med 2007;32:1–10. DOI: 10.1016/j.amepre.2006.08.028

93. O'Connor MJ, Whaley SE. Brief intervention for alcohol use by pregnant women. Am J Public Health 2007;97:252-8. DOI: 10.2105/AJPH.2005.077222

94. Miller WR, Sanchez VC. Motivating young adults for treatment and lifestyle change. In: Howard, G. ed. Issues in Alcohol Use and Misuse in Young Adults. Notre Dame: University of Notre Dame Press, 1994; 55-81.

95. Abel EL. Fetal alcohol syndrome in families. Neurotoxicol Teratol 1988;10:1-2. https://doi.org/10.1016/0892-0362(88)90060-8

96. Burd L, Martsolf JT, Klug MG, Kerbeshian J. Diagnosis of FAS: a comparison of the Fetal Alcohol Syndrome Diagnostic Checklist and the Institute of Medicine Criteria for Fetal Alcohol Syndrome. Neurotoxicol Teratol 2003;25:719-24. https://doi.org/10.1016/j.ntt.2003.07.015

97. Coriale G, Fiorentino D, Di Lauro F, Marchitelli R, Scalese B, Fiore M, et al. Fetal Alcohol Spectrum Disorder (FASD): neurobehavioral profile, indications for diagnosis and treatment. Riv Psichiatr. 2013;48:359-69. DOI: 10.1708/1356.15062. DOI: 10.1708/1356.15062

98. Young JK, Giesbrecht HE, Eskin MN, Aliani M, Suh M. Nutrition implications for Fetal Alcohol Spectrum Disorder. Adv Nutr 2014;5:675-92. DOI: 10.3945/an.113.004846

99. Poitra BA, Marion S, Dionne M, Wilkie E, Dauphinais P, Wilkie-Pepion M, et al. A school-based screening program for fetal alcohol syndrome. Neurotoxicol Teratol 2003;25:725-9. DOI:10.1016/j.ntt.2003.07.007

100. Petkovic G, Barisic I. Fas prevalence in a sample of urban schoolchildren in Croatia. Reprod Toxicol 2010;29(2):237-241. DOI: 10.1016/j.reprotox.2009.11.006

101. Kuo HT, Wu HP, Li Q, Zhou FC, Morisky DE, Lee ML. In school study of prevalence of fetal alcohol spectrum disorder in east Taiwan. Alcohol Clin Exp Res 2012;36(SupplS1):280. DOI: 10.1111/j.1530-0277.2012.01917.x

102. Lee HK. Epidemiology of Fetal Alcohol Syndrome in Korea: an active case ascertainment study. Alcohol Clin Exp Res 2012;36(SupplS1):212. DOI: 10.1111/j.1530-0277.2012.01917.x

103. Petkovic G, Barisic I. Prevalence of fetal alcohol syndrome and maternal characteristics in a sample of schoolchildren from a rural province of Croatia. Int J Environ Res Public Health 2013;10:1547-61. DOI: 10.3390/ijerph10041547