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Use of Alcohol during Pregnancy in France: Another French Paradox?

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Abstract

Drinking alcohol during pregnancy in human may cause Fetal Alcohol Syndrome (FAS) in the worst cases or Fetal Alcohol Effects (FAE) in the lightest cases. FAS inevitably induce growth retardation, craniofacial as well as congenital malformations and irreversible cognitive and behavioural deficits in the children whereas FAE lack malformations but are still accompanied by lifelong cognitive deficits. Although scientific knowledge about the effects of ethanol during early brain growth period had considerably increased over the last decades, the problem of the consequences, the cost and the care of infants exposed to alcohol during pregnancy remains spread worldwide. In many industrialized countries including France the country of the first description of FAS in 1968, the sanitary problem is clearly not a public health priority and thus still not yet resolved. Indeed, research in France on this public health problem remains inadequately organized and funded. Nevertheless, some efforts have been recently done by some scientists, clinicians and others and we believe that beside primary prevention towards the lay persons, the most consensual and less ambiguous health message should remain "No Alcohol during pregnancy". In this review, after a short history of FAS/FASD, we compiled data concerning incidence, social cost, national health policy and organization of research in FAS/ FASD field. We deliberately emphasize the situation in France as our working team is based in this country and we choose to document this review with available data from some official internet sites.

Keywords: Ethanol; Prenatal; SAF; FASD

Introduction

Alcohol (ethanol) might be called a "dirty drug" because it does not imply a specific type of membrane receptor to be effective in contrast to other psychoactive substances, although the activity of the GABAA receptor is probably modified as soon as the first glass of alcohol (ca. 3 mM ethanol) [1]. Once in the body, ethanol has no biological barrier because it has the property to be soluble in both water and lipids. Therefore, ethanol diffuses passively throughout the body. As a matter of fact, ethanol when consumed by pregnant women easily crosses the placental barrier and reaches the fetus brain. Nor the fetus, the embryo nor its physiological side structures do have ethanol metabolizing enzymes (i.e., ADH, Alcohol dehydrogenase). Therefore, the action of alcohol on the fetus persists much longer than in the mother's body. Specifically, one may almost consider that the fetus is literally sink in an "alcoholic amniotic fluid". The effects of alcohol are multiple, polymorphs and largely irreversible for a large number of them, making alcohol a powerful teratogenic substance. Indeed, ethanol appears as the most dangerous drug for the fetus and thus the most teratogenic. Despite our present knowledge of the deleterious effects of alcohol and several prevention campaigns in France, there are still about 25% of French pregnant women who report drinking alcohol at some time during pregnancy including those consuming relative moderate levels of alcohol by Blondel et al. Surprisingly, the health recommendation message of "zero alcohol" consumption during pregnancy is presently raised as an issue in France while several clinical and preclinical studies indicate that even low to moderate ethanol exposure during brain development induces several enduring deficits in the adult such as learning and memory impairment. In consequence, the recommendation for total abstinence remains poorly understood by women in France, who finally know little about the consequences of alcohol consumption on the unborn children. Interestingly, the sources of information of these women about the effects of alcohol consumption during pregnancy can be numerous, but intriguingly their own mothers remain their most credible source [2].

Historic Flashback

The first clinical report about Fetal Alcohol Syndrome (FAS) was published in 1968 by Paul Lemoine, a French pediatrician. He noted that some children had common facial features. After interviews with nurses and mothers, he finally found the common point: all children's mothers were "heavy" alcoholics. It was the first time that the large array of neurodevelopmental and physical disturbances in children of women who drink alcohol during pregnancy was described. However its report was not published internationally and thus received little attention (Les enfants de parents alcooliques: anomalies observées à propos de 127 cas). Translated as (Outcome of children of alcoholic mothers: anomalies observed in 127 cases). His major challenge was then to convince people and politicians that alcohol could have such toxic effects. The task was evidently rather difficult in a country where wine is so deeply present, historically, economically and culturally. Finally, it is not before 1973 and the review written by two American morphologists, Jones and Smith that the name of Fetal Alcohol Syndrome was introduced to clinician and pre-clinician scientists [3]. Jones and Smith identified "craniofacial, limb, and cardiovascular defects associated with prenatal onset growth deficiency and developmental delay" in 8 independent children form 3 different ethnic groups but all born from alcoholic women. The type of malformations observed indicated a prenatal origin of the disease. This work,

published by a team of researchers of the University of Washington in Seattle in 1973 under the direction of Dr Smith D (Drs. Kenneth Jones, David Smith, Christy Ulleland, and Ann Streissguth) was the first study to be presented internationally. Since then, it appears that not all children developed a full blown fetal syndrome. Therefore, another category of somehow lighter disturbances has been first referred to fetal alcohol effects (FAE) in the eighties, then to alcohol-related neurodevelopmental disorders (ANRD) in the nineties and finally to fetal alcohol spectrum disorders (FASD) in the years 2000. This repeated changes in the disease appellation revealed the difficulty for both the clinicians and the scientists to embrace all cases of disturbances induced by prenatal alcohol exposure in one single name. Indeed, a simple picture is now commonly accepted which point out that cases of FAS are only the tip of an iceberg as proposed by A. Streissguth [4]. Specifically, it appears that alterations induced by prenatal alcohol exposure are so diverse, occurring even at low or moderate levels of ethanol that one should consider the ensemble of induced problems as a continuum. The category of patients without the full blown syndrome represents a complex clinical entity in which children do not show all the characteristic features of FAS. In general, these children showed only part of the FAS symptoms while their mother drunk alcohol during pregnancy. For example, some of them have slight growth retardation with only some of the known craniofacial abnormalities. Nevertheless, the most robust disturbances which occur in all category of children that have been exposed at some point to any level of alcohol during gestation are life-long learning and behavioral deficits, which furthermore may be noticeable only after few years and thus being unappreciated by the clinicians at birth. Importantly, these late consequences are almost always related to educational underachievement and poor social interactions. These observations raise then a first problem concerning the correct identification of newborns at risk because their mother had drink alcohol at some point during pregnancy and the care that medical practitioners should bring to them as early as possible.

Indications from Epidemiology: FAS and FASD Incidences

In European and American countries it is assumed that still a significant number of pregnant women continue to drink alcohol at some times throughout pregnancy. In North America, such figure reaches 10 to 20 % in the USA and 13.9% in Canada (Canadian Community Health Survey, 2003). In France it is about 25% while in Uruguay it reaches 40% and 50% in some regions of Italy for example. This latter high figure is not unique and does not concern only Italy as we will show below. FAS incidence in France is about 0.5 to 3/1000 live births with important regional variability. Indeed, when studies are carried out in specific regions both numbers of pregnant women who still consume alcohol and FAS/FASD incidence is much higher than the national average number currently accepted by the community. Some parts of France are highly impacted by ethanol consumption during pregnancy. The Réunion Island in the Indian Ocean is a good example but also Picardy and Brittany. FAS incidence in this area may reach up to 4 to 8/1000 live births. In USA, the Center for Disease Control and Prevention (see CDCP website) identified 0.2 to 1.5 infants with FAS for 1000 live births with also great area differences throughout the country. More recently, the same organization reported FAS in 0.3 / 1000 children from 7 to 9 years of age and analysing in-person assessment of school-aged children in different American communities estimated FAS as 6 to 9/1000 children [5]. In Canada the exact prevalence of FAS remains unknown but reports [6] from Sampson et al. estimated the incidence of FAS to range from 2.8 to 4.8 / 1000 live births. Like in other countries, incidence is higher in some area (see PHAC website). Furthermore, higher incidence in some specific ethnic group was also noted although it is largely acknowledged that all races are susceptible. A recent report [7] from Burns and coll showed that in Australia birth prevalence rates of FAS ranged between 0.01 and 0.68/1000 live births, but these values are acknowledged by the authors to be clearly underestimated. Maybe more interesting is the case of Japan which appears slightly different from other countries since the prevalence of FAS (and FAE-FASD) in this country has been estimated to be less than 1/10 000 live births according to a 1998 review by Tanaka [8]. Unfortunately this is the only review presently available for Japan although many researchers are working in the field of prenatal alcohol exposure both at clinical and preclinical levels. An article in 2005, claimed to be the first report concerning FASD in this country, found 10 % of children with FASD in a group of alcoholic pregnant women who consumed alcohol during pregnancy. In a more recent study [9] by Miyake et al. it is suggested that 1.0 g per day of ethanol consumption is the lower limit correlated with preterm birth. In Eastern Europe, there is no precise figures for FAS except for children living in orphanages or those who have been adopted. American researchers clearly demonstrated in a recent meta-analysis that prevalence for FAS/FASD among children in child-care systems was 60 / 1 000 and 169 / 1 000 for the youth Lange et al [10]. Beside this specific latter population, it is noteworthy that a recent publication indicated that rates of FASD among first grade children in a representative middle-class community in the American Midwest are substantially higher than most previous estimates for the general populations of the United States, Europe, or Canada May et al [5]. Using three techniques to estimate prevalence, the authors determined that between 6 and 9 children per 1000 have FAS in this community cohort of school children, and 11 to 17 per 1000 children have partial FAS. The total prevalence rate for FASD is thus largely underestimated and may reach 24 to 48 children per 1000. It is generally assumed that in France the figure for FAE or FASD reaches 1/100 lives birth, meaning that 7 000 to 8 000 infants per year are born being affected by alcohol at some point. Few estimates for the full range of FASDs are available for Canada but on the basis of three population studies by Sampson et al. [6] estimated the incidence of a combination of FAS and FASD to be at least 9.1/1000 live births. The Public Health Agency of Canada recognized that FASD affects about 1% of people, meaning that about 300,000 persons are living with FASD. Finally and globally, based on community studies using physical examinations, experts estimate that the full range of FASDs in the United States and some Western European countries might be as high as 2 to 5 per 100 school children (see CDCP website). Back to earlier estimation studies made in the late eighties, beginning of the nineties, the prevalence rate was between 0.33 and 1.9/1000 live births in the USA, with a more precise figure of 43/1000 (4.3%) among babies of heavy drinkers. All these data clearly show that the problem of alcohol consumption during pregnancy is similar in almost all industrialized countries and that in almost every country there is area or ethnic communities that are specifically endangered by prenatal alcohol exposure. More importantly, several studies showed that many cases of alcohol exposure during pregnancy reveal themselves few years after birth, literally when children enter the school program. As last example, in a cohort of 2 600 FAS followed other 18 years, it appears that 14% of them were exposed to 1 to 8 glasses per week and that 50% of them had normal IQ at preschool age but 100 % had cerebral dysfunction at the age of 10 by Astley. Therefore and comparatively to other industrialized countries, the figures for France are close to what is

known elsewhere making France not a special case for FAS and inversely, making FAS a rather worldwide distributed disease. Therefore, communication to the lay public and to politicians about incidence, number of cases and percentage of population concerned by ethanol during pregnancy should be carefully conducted and edited in a clear "take home" message. It must however be kept in mind that diagnosis of FAS remains a difficult task for the clinicians especially when the typical features of the full syndrome are not present. Therefore, and as stated in a recent French report published in the "Bulletin Epidémiologique Hebdomadaire" (Weekly Epidemiology Bulletin) the figures of prevalence are underestimated. More specifically, the authors wrote on a feasibility study of the monitoring of FAS at birth in France. They showed a significant underreporting which was finally very operator-dependent. Importantly and maybe not surprising, the study concluded that the lack of a strong politics of screening and diagnosis in the context of a care network makes the setup of a reliable system of FAS monitoring rather impossible proposed by Bloch et al [11-12]. A first French paradox appears here: the country of the FAS first report does not seem to consider itself as a country where FAS exists in the same order of magnitude as other industrialized country. In this context, it is important to notice that there is no strong political willing to introduce courses and training about FAS in medical and nursing schools. In 2013 the French High authority for Health proposed a record recommendation on FAS regarding systematic screening pregnant women for their alcohol intake (HAS website).

Two guidelines have been done in France to help health care professional to deal with FAS and learn more about how discussing this topic with their patients.

Which Recommendation needs to be applied?

If a women had a first child diagnosed as FAS, the risk of having a second one is of 75% if she continues drinking during pregnancy, whereas a woman who drinks high quantity of alcohol has only a 5 % risk to give birth to a full blown FAS by Burd et al [13]. Although FAS is mainly observed for high doses of alcohol (superior to 2 glasses / day or during acute intoxication superior to 4 glasses in one occasion), it is now clearly established that even moderate or low doses of alcohol is responsible for some neurological alterations in the fetus. It is then difficult to give clear-cut recommendations defining minimal doses to be acceptable or maximal doses not to be reached without taking the risk of inducing any kind of malformations and future deficits. Studies from large cohorts clearly showed that intensity of cognitive deficits on the long term are correlated to the intensity and duration of fetal alcohol exposure, although individual predictability remains impossible. Indeed, risks are depending upon many other factors such as the level of blood alcohol content (BAC), time of these high BAC, duration of exposure, multiple drug consumption (nicotine, cannabis, cocaine..), age of the mother, socio-economic status of the family, polymorphisms of alcohol metabolism for both the mother and the fetuses. Nevertheless, it is important to remember that stopping alcohol consumption during pregnancy have been always shown to be beneficial to the newborn. This was reported in [9] the study of Miyake et al. and recently in [14] Gaskins et al. In the first paper, the authors compared alcoholic women who continue drinking alcohol during pregnancy with those who stopped drinking during pregnancy. Interestingly, the second group of women had a lower risk of preterm birth than the first group. In the second study it is reported that drinking alcohol before pregnancy at low to moderate level (≤12 g/d) does not increase the risk of spontaneous abortion or stillbirth. These two studies suggest that it is the consumption during pregnancy which is deleterious for preterm, abortion or still birth consequences. Therefore and to be on the safe side, stopping alcohol consumption even before being pregnant would be much more beneficial even if a previous child have been diagnosed for FAS. In this context, the Health Regional Agency of Picardy in France ran a prevention campaign with leaflets and posters directed toward both professionals and lay public (Figure 1) to emphasize this new type of prevention message, i.e. stop drinking if pregnancy is desired and do not propose alcoholic beverages to pregnant women.

Figure 1: Poster produced for a prevention campaign by the ARS Picardy. This poster was specifically dedicated to the message of "zero alcohol before conception". From top to bottom, the drawings illustrate pregnancy (Grossesse) and breast-feeding (Allaitement). The two sentences in the green rectangle can be translated as: "Do not consume alcohol before and during your pregnancy or during breast-feeding" and "Do not invite pregnant or breast-feeding women to drink alcohol.

Socio-economic Cost of Alcohol, FAS/FASD in Industrialized Countries

One obvious consequences of FAS/FASD is its enormous costs for the society. In USA, the lifetime cost for an individual with FAS has been estimated to US $ 2 million. In Canada, the annual cost of the global health care problems related to prenatal alcohol exposure is over $5 Billion. A review of the literature have been performed by Navarro and colleagues to estimate the costs of FAS including data on harm to others. Although the authors clearly described the differences, the bias

and the way of counting the cost in the studies they collected, it gave an interesting view of the situation. Indeed, they reported only 16 studies concerned with the effective social cost of FAS/FASD, published between 1985 and 2009, including 12 studies for the USA, 3 for Canada and one for Sweden. At nationwide level, the social cost of FAS/FASD is between $USD 75 million to $USD 3.2 billion for USA, depending on the number of parameters included in the cost estimation. For Canada, the range could be between $CAN 344 million to 5.3 billion. Regarding France, the socio-economic consequences of FAS/FASD has never been estimated to our knowledge. However, the global socio-economic consequences of alcohol consumption look simply tremendous. In 2015, a report from the French General Direction for Health and OFDT (French Observatory for Drugs and Toxicomania) written by Pr Kopp, an economist from Paris Panthéon-Sorbonne University and assistant Pr Fenoglio from Nancy University indicated a total cost for the French community of €120 billion per year (reaching almost the cost of smoking tobacco). In comparison, other illegal drugs cost €8.7 billion per year to the French society. Fifteen years ago, the same authors in a report written for the same organization noted that alcohol represented 52 % of the total social costs for licit and illicit drugs in France. Furthermore, in 2012 the total sanitary and social costs for alcohol related problems were evaluated to be €20 billion (http://tempsreel.nouvelobs.com; the Bulletin épidémiologique hebdomadaire de l'Institut de veille sanitaire (InVS)). Interestingly, this last figure is almost the same that what legal alcohol selling bring to the French government and although the comparison may look simplistic in nature, it appears that the gain on one side in terms of economy is lost the other side in terms of sanitary and social costs. This is to our point of view another French paradox.

Some Efforts of Prevention-milestones in Some National Policy

In 1978, the Third Special Report to US Congress on Alcohol and Health: Fetal Alcohol Syndrome was published by the Department of Health and Human Services and the National Institute of Alcohol Abuse and Alcoholism (NIAAA). This was the first time FAS became an integral part of this specially commissioned report to the US Congress. Contents included etiology, symptoms, physical signs and physical damage to organs, psychological aspects, economic costs and current research (http://www.faslink.org). Throughout the 1980s, there were many published articles in both the scientific and lay press about the harmful effects of maternal drinking during pregnancy, and in 1988 the government passed. At this point, the lay public – including trial attorneys – should have known about the potentially damaging effects of maternal alcohol use. In this context, the US government adopted in 1988 the Alcoholic Beverage Labeling Act (USC 27, Section 213), a law mandating that warning labels appear on all alcoholic beverage containers stating that "According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects" (Figure 2A). Interestingly, this warning message refers only to the case of birth defects due to alcohol consumption and thus totally neglects the risk of lifelong cognitive deficits. In 1996, the US Institute of Medicine reported to the Congress that "Of all the substances of abuse (including cocaine, heroin, and marijuana), alcohol produces by far the most serious neurobehavioral effects in the fetus." Surprisingly, in France, the country in which FAS has been reported for the first time, it is not before 2005 that the ministry of health changed the Public Health rules by imposing a warning message on every alcohol containers. Specifically, the law article L.3222-2 of the Public Health code (extracted from law N° 2005-12 of the 11 of February 2005) specified that each alcoholic beverage container should mention a sanitary message stating that pregnant women should not drink alcohol. Of course, such message does concern only beverages indicating a volume alcohol level superior to 1.2° which thus does not include alimentary complements such as chocolate or hydro-alcoholic solution. On the 3rd of October 2006, the new rule was put into action with final precisions concerning the size of the warning label to be put on every conditioning containing alcohol. It is noteworthy that due to the very strong lobby from the alcohol industry in France and the numerous political representatives at national level from the wine producing regions, the final pictogram on each bottle has a very small size (4mm diameter) and is finally barely visible (Figure 2). It is nevertheless a message of high precautionary principle which was accompanied with a prevention campaign stating "zero alcohol during pregnancy" or " drinking alcohol during pregnancy even in small quantities can cause serious consequences on the children's health" which appeared on every bottle. Hopefully, the recent report edited in 2016 by the French National Academy of Medicine (see http://www.academie-medecine.fr) on fetal alcohol syndrome which includes clear recommendations will help politicians to take strong decision in a near future. Nevertheless, it took about 18 years to the French to follow the example of USA on public health policy. Another interesting French paradox.

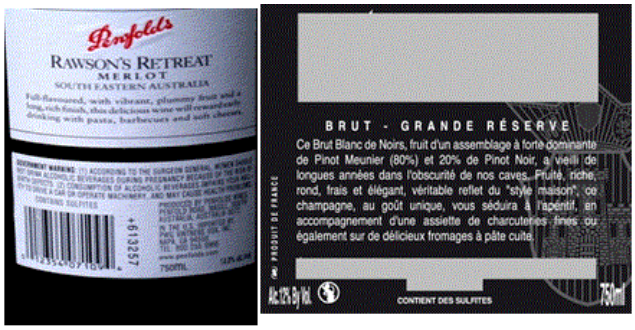

Figure 2: Examples of labelling found in alcoholic beverage containers. On the left, an example from an Anglo Saxon country. The warning health message is made of three distinct lines and described the effects of drinking alcohol during pregnancy and also the danger for car driving or operating machinery. On the right side is the French warning message. It is a small logo barely visible and of comparatively small surfaces in regard to that devoted to advert for the trade (grey rectangles).

Research on FAS or FASD: Where Do We Stand?

In order to better understand the clinical picture of FAS or FASD, strong and reliable preclinical researches should be performed. In this context reliable animal models of FAS/FASD should be developed and analysed. Presently, many models of fetal alcohol exposure can be found throughout the literature, mostly done in rodent's laboratory animals. In our laboratory, we developed a rat model of perinatal alcohol exposure through drinking solution (10 % ethanol V/V) intoxicating first the dams for few weeks and continuing the exposure throughout gestation and lactation periods. Although this is a model of forced ethanol exposure, it has the advantage to be easy to handle and to cover the human equivalent of the three trimesters of gestation. Indeed, we decided to model the relevant cases of long-lasting

intoxicated pregnant women. Another advantage is the relative moderate level of blood alcohol content reached by dams, which after few weeks of intoxication auto regulate their consumption of alcohol (ca. 100 mg/dl) allowing us to study the full developmental aspect of moderate ethanol exposure throughout gestation. With such model, we were the first to show specific long term physiological disturbances besides cognitive ones already described in the literature. Specifically our first studies demonstrated that breathing function was highly disturbed in terms of endogenous respiratory rhythm generation (instability and respiratory phase durations being abnormal) and in terms of adaptive response to low oxygen environment (lack of chemoreflexes) in the offspring by Dubois et al [15]. Furthermore and importantly, the capacity of the respiratory network to develop long lasting network plasticity in neonatal rats after repeated short episodes of low oxygen was reversed to a long lasting depression of breathing, suggesting a link between prenatal alcohol exposure and failure of the respiratory system to cope with repeated episodes of hypoxia in newborns Kervern et al [16]. Besides these intriguing effects of prenatal alcohol exposure on the function, we also revealed sensitization of the respiratory network to acute alcohol. Interestingly, most of the reported effects were due to an increase in the glycinergic inhibitory system within the bulbar respiratory network. In terms of cognitive function and cellular mechanisms of learning and memory, much have been shown concerning synaptic plasticity failure or reduction in the hippocampus and learning deficits in a large range of prenatal and/or perinatal model of ethanol exposure. Using the same model as for the study of the respiratory system, we brought new data by revealing that not only synaptic long term potentiation (LTP) is reduced after ethanol but that concomitantly, long term depression (LTD) is dramatically increased. With a combination of pharmacological approaches, biochemistry and molecular physiology we suggested that both the NMDA component of the glutamatergic neurotransmission and the GABA inhibitions via the GABA-A receptors are concomitantly disturbed although each through a different cellular mechanisms [17]. We also demonstrated the long-term effect of this ethanol exposure such as an increased vulnerability to both the rewarding and the stimulant effects of ethanol but also of other drugs of abuse, supporting then the known epidemiological and clinical data. Today, it seems of particular importance to determine the threshold of ethanol exposure and the time window of exposure that may induced some disturbances, notably at the cognitive level. Indeed, in too many cases either in front of politicians or lay public the question of the threshold is redundantly asked. Therefore, it really appears that an answer should be bring to those people. It is our impression and interpretation that bringing such an answer will reinforce the bonds between researchers and lay public in a general manner. In terms of scientific knowledge, it is now clearly demonstrated by both preclinical and clinical studies that exposure to almost any level of alcohol during brain development is deleterious to the offspring. Consequently, the matter is now to i) better understand the mechanisms of ethanol in the brain during pregnancy and responsible for all the known damages, ii) find reliable biomarkers of prenatal ethanol exposure that may help clinicians in the detection of FAS and iii) to help reversing the situation of these children. Therefore, FAS and FASD are requiring more analysis and studies and thus a clear and strong scientific plan should be put on. In the USA, a great deal of efforts has been already made and since the creation of the NIAAA in 1972 many research programs have been funded and were successful to increase our knowledge. The US through NIH and NIAAA organizations are able to invest more than $USD 440 million only for alcohol research. As an example, the recent Collaborative Initiative on FASD (CIFASD, see the website) embedded 22 research sites located in USA, Finland, Ukraine, England and Russia, to perform basic, behavioral, and clinical research to "inform and develop effective interventions and treatment approaches for FASD". With such a consortium the coordination between basic, clinical and translational research on FASD become possible. The same is true for Canada, and at least in 2013, the Harper government invested in FASD projects. In a first project, diagnosis tools were to be developed for clinicians, and in a second project a better analysis of the population is proposed to know how much Canadian people are living with FASD (see the website of CanFASD). In France and somehow in contrast with north American countries, there is still no clear decision made by the different governments on this specific disease, except for only one wave of call for funding through the national ANR SAMENTA program, standing for Mental Health and Addiction, in 2006 which mentioned FAS within all types of mental diseases included into this program. Indeed, among the scientific program funded through this call, only one did concern Alcohol research and none concerning FAS/FASD was funded. Another round 6 years later, in 2012 funded one project (over a total of 13 accepted) on alcohol while none was funded in 2013 over 14 accepted project. Only one wave of call for funding through the European ANR program in 2015 (Joint Transnational Call, JTC 2015, for European Research Projects on Neurodevelopmental Disorders under the ERA-NET NEURON II) clearly mentioned FAS within all types of mental diseases included into this program. It is noteworthy that a recent publication reported that research on addictions does not appear as a high priority in France [18] and that cultural, popular temperance and alcohol policies may play an important role in the present low priority for alcohol research in this country. Furthermore, research teams in France which are more or less specialized in FAS or FASD do not really exist per se, although many researchers are interested in studying the effects of alcohol. In France, not a single research team is acknowledging as a leading group for alcohol effects at both clinical and preclinical levels. Indeed, neither INSERM nor CNRS, the two French national institutions for research, do include one such team of research in their rank except maybe our team which is the only one fully dedicated to alcohol research. The landscape of French research in the effects of alcohol seems more a patchwork of individuals with a complete lack of dedicated institute for example, rather than a coordinated network. Only in 2015, did Pr Naassila and his colleagues from Amiens, took the opportunity to ask for funds from MILDECA (Interministerial Mission for Combating Drugs and Addictive Behaviours) in order to create a scientific French network about alcohol research in France (including FAS/FASD). Cohorts of patients are also present in France and some of them are clearly identified but remain not well coordinated and not sufficiently included in clinical protocols. Anyway and as positive example, the civilian association SAFFRANCE among others participates with local representatives and MILDECA to the creation of a center of reference for FAS-FASD in the Réunion's Island in 2016 thanks to his president's efforts Dr Lamblin Denis. Another one is planned in the French region of Aquitaine, near Bordeaux. Is the situation of research on alcohol in France another paradox for a country highly concerned with alcohol consumption?

Conclusion

The effects of alcohol on the fetus are highly diverse and complex. Nevertheless, increasing our knowledge about all these effects may lead to identify different ways to protect the children. Alcohol's effects are totally irreversible and this should be taken into account in prevention

messages. FAS is clearly identified as the first cause of mental retardation which is furthermore absolutely preventable or at least largely controllable if one can convince pregnant women to reduce their consumption of alcohol during pregnancy, as it is done for tobacco. The most important is not only to look for signs of FAS but also to learn more about high level and low to moderate alcohol levels. Because these children may carry an irreversible long-life handicap, they must be better identified and diagnosed and then directed to specific care unit. The most difficult thing to sustain for them (and also for the family) is not being diagnosed early and entered into a medical care program. Different actions of prevention should be coordinated between pregnant women, health professionals (nurses, midwifes, doctors, pharmacists, surgeons) and the socio-medical actors (psychologist, social helpers) The present consensual and worldwide clear prevention message: "zero alcohol during pregnancy" can be easily adapted to the young population by "zero alcohol once the couple decided to get a baby, and stop proposing alcohol to a pregnant woman". It is also necessary to remind the young women that binge drinking is probably even more dangerous for them and for the baby. The most insurmountable challenge for the future, at least in France, is to fight against the denial of the general population (and health care professionals) about the deleterious effects of alcohol which create not only damages for the patient but also to friends and family and the whole population. An even more insurmountable challenge is of course the denial toward alcohol from the health professionals themselves. Finally, we believe science should be better organized in France and should get more support from both the government health representatives and some foundations.

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