Universitat de Girona

FACULTY OF MEDICINE

FINAL DEGREE PROJECT

# INTRODUCTION OF THE GREEN PAGE AS A TOOL FOR QUANTIFICATION OF PRENATAL ALCOHOL EXPOSURE IN THE REGION OF LA GARROTXA

## Garrotxa Pediatric Environmental Health Specialty Unit

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## ABSTRACT

**Introduction:**

The preconception period and pregnancy are critical periods vulnerable to environmental risk factors, such as alcohol exposure. The campaigns of the World Health Organization and the Spanish Health Ministry encourage the creation of tools to improve health during pregnancy and the pre-conception period, such as the Green Page.

Alcohol has an important role in our society, the intake of this liquid has a marked cultural and social well-established character. Alcohol consumption during pregnancy and the preconception period is the leading cause of preventable school failure and developmental disorders, such as fetal alcohol syndrome and fetal alcohol spectrum disorders (FASD).

**Objective:**

Quantify the prenatal alcohol exposure in the region of La Garrotxa and determine the frequency of embryos/fetuses at high risk of developing FASD.

**Design and methods:**

Clinical, observational, longitudinal and descriptive study to evaluate prenatal alcohol exposure in pregnant couples during their first visit of the pregnancy follow-up and control program. Exposure data obtained by a clinical interview tool, the Green Page

**Results:**

A total of 616 pregnant couples were recruited, with an increasing number of couples each year. Along the total period of the study, a 54,8% of all pregnant women drank alcohol during the periconceptional time. Those who drank, 84,7% quit drinking during pregnancy. A 13,9% drank more than 6 drinks per week, and 2,7% had ≥20g/day. For those who kept drinking, 89,0% drank less than 1g/day, and only 1,8% drank more than 5g/day. Only one pregnant woman kept drinking more than 6 drinks per week and one drank more than 20g/day. 2% of the women had 2 or more binge-drinking episodes and 1,4% had ≥3 episodes.

A 72,1% of the fathers drank during spermatogenesis. Of the whole, 10% drank ≥20g/day and 2,7% of men had a risk alcohol habit (≥40g/day).

A total of 2,4% embryos/fetuses were at high risk of developing FASD (≥20g/day and/or ≥3 binge drinking episodes), but in a less restrictive criteria (>6 drinks/week and/or ≥2 binge drinking episodes) this would rise to 5,8%.

The whole consumption of alcohol for both pregnant women and couples decreased during the period of study, and we found a statistically significant reduction of alcohol exposure.

**Conclusion:**

The Green Page is a useful, easy-to-use and reproducible clinical tool for detection, prevention and alcohol consumption management. Fetal alcohol exposure is high in the county of La Garrotxa.

**Key words:**

Alcohol; pregnancy; periconceptional period; fetal alcohol syndrome; fetal alcohol spectrum disorders; binge-drinking.

## ABREVATIONS

| | |
|---|---|
| AEP | Alcohol-Exposed Pregnancy |
| AFR | African Region |
| AMR | Region of the Americas |
| ARND | Alcohol-Related Neurodevelopmental Disorder |
| BAC | Blood Alcohol Concentration |
| CNS | Central Nervous System |
| EDADES | Encuesta sobre Alcohol y otras Drogas en España |
| EMR | Eastern Mediterranean Region |
| EU | European Union |
| EUR | European Region |
| FAS | Fetal Alcohol Syndrome |
| FASD | Fetal Alcohol Spectrum Disorder |
| GP | Green Page |
| IAC | Internationally Adopted Children |
| NIAAA | National Institute on Alcohol Abuse and Alcoholism |
| PAE | Prenatal Alcohol Exposure |
| PEH | Pediatric Environmental Health |
| PEHSU | Pediatric Environmental Health Specialty Unit |
| pFAS | partial Fetal Alcohol Syndrome |

| | |
|---|---|
| SEAR | South-East Asia Region |
| SFF | Sentinel Facial Features |
| WHO | World Health Organization |
| WPR | World Medical Association |
| WPR | Western Pacific Region |

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# 1. INTRODUCTION

## 1.1. PEDIATRIC ENVIRONMENTAL HEALTH

The Environmental Pediatrics or Pediatric Environmental Health (PEH) addresses the environmental factors that affect the health of children, from the periconceptional period to the end of adolescence (1)(2)(3).

The health of a person is determined by the interaction of the environment (biological, physical, chemical, social and psychosocial) with the genes, shaping the individual we know (4).

The World Health Organization (WHO) in 1993, due to the progressive contamination of environmental ecosystems and the growing social concern about the potentially adverse effects on human health, defined the Pediatric Environmental Health as:

a) the aspects of human health, including the quality of life, determined by the interactions of the physical, chemical, biological, psychic and social environmental agents; and

b) the theoretical and practical aspects to evaluate, correct, control, modify and prevent environmental factors or agents that, potentially, adversely affect the health of present and future generations (5).

In the last decades, the impact of the environment on human health has become evident. Prominent international organizations, such as the WHO and the European Union (EU), have expressed their concern regarding the air pollution that our ecosystem is currently suffering from on various levels. From the air we breathe, to the water we drink, through the food we eat and even the socio emotional context in which we live (6).

Children are the most affected by this degradation of our environment, because despite representing 15% of the world's population, they receive 43% of the burden of environmental diseases (7).

Pollution and associated diseases affect developed and undeveloped countries. Children, as we have already said, are especially vulnerable to pollution in order to develop adverse effects (table 1) (8)(9).

*Table 1. Characteristics that determine children's vulnerability to environmental pollutants* (10).

| |
|---|
| Biological immaturity (anatomical and functional) |
| Higher energy-metabolic consumption |
| Social Behavior and Own Behaviors |
| Higher life expectancy |
| Impact of shorter height |
| Null and void decision-making capacity |

### 1.2. CRITICAL PERIODS ON HUMAN

The preconception period, pregnancy and lactation, constitute the stages of greater vulnerability of the individual to environmental risk factors.

A critical period is defined as the especially sensitive time interval during which exposures or events may interrupt or interfere with the physiology of a cell, tissue or organ. These periods are characterized by a marked cellular proliferation and the development of numerous changes in the metabolic capacities of the organism. Certain exposures during these windows can result in permanent and irreversible adverse effects (11). The periconceptional stage, pregnancy and the first years of life constitute especially critical stages for the optimal development of individuals.

There is considerable consensus that environmental influences during critical periods of pregnancy development have a considerable impact on human development. Exposure to alcohol and other illegal drugs during pregnancy is underdiagnosed and constitutes a taboo for professionals. In addition, alcohol consumption has very little perception of risk among families (12)(13).

Organogenesis period corresponds to the most delicate phase and external influences which will produce greater adverse consequences. During the period of organogenesis (12 weeks), teratogenic drugs cause abortions and congenital malformations (see figure 1).

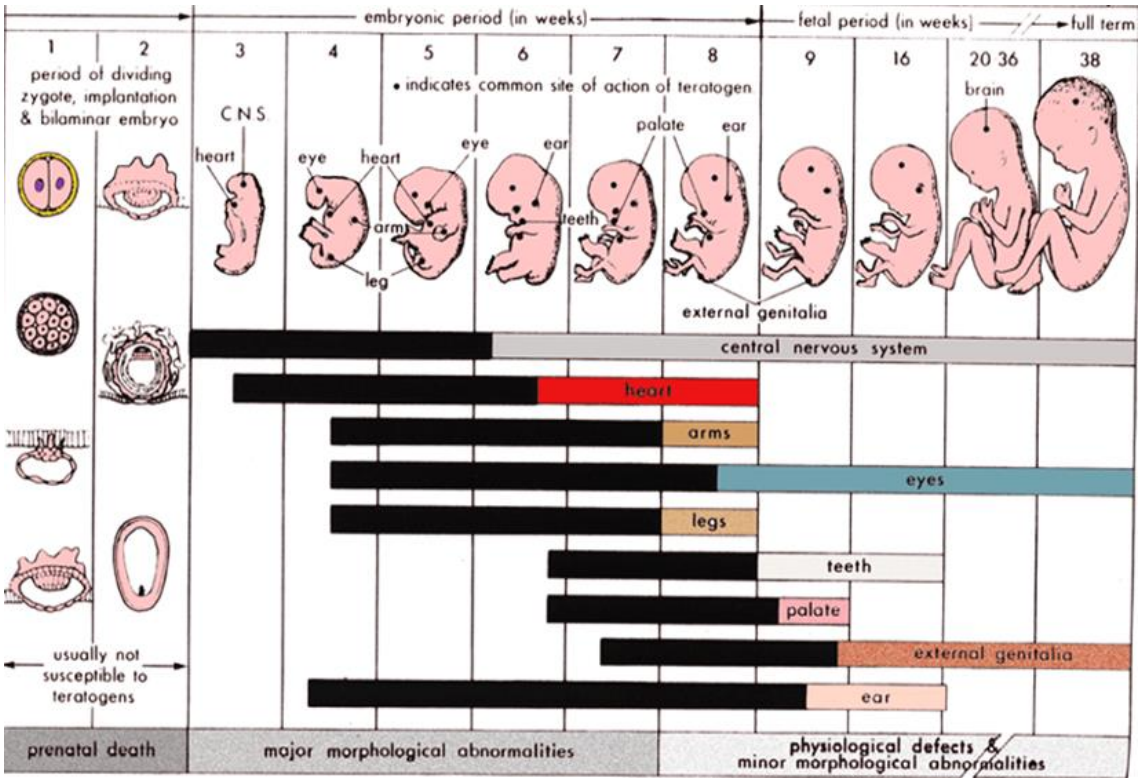


*Figure 1. Developmental progression and susceptibility to teratogens and fetal loss* (14).

This is a period especially sensitive to teratogens since cell division is very high and since it is such an early stage of pregnancy the damage is very structural. In addition, the pregnant couple does not usually know the diagnosis of pregnancy until almost the end of this period so the risk of exposure to teratogens and other toxic substances is greater (15)(figure 2).

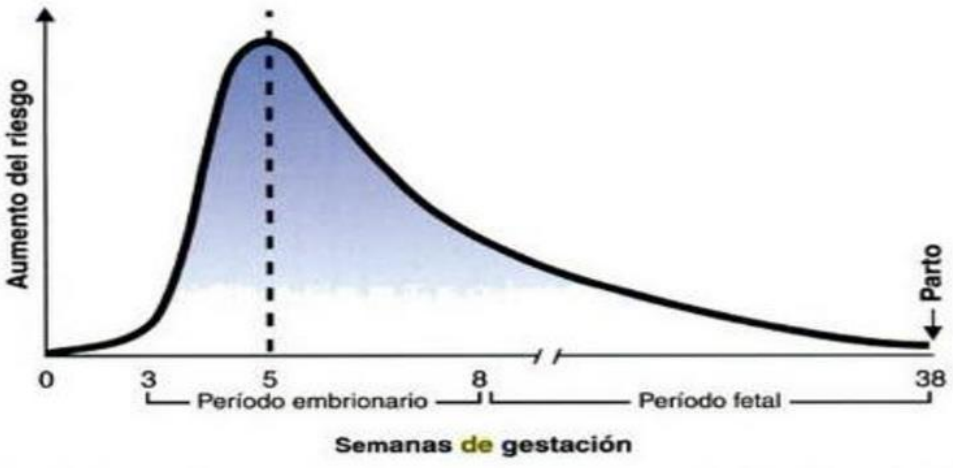


*Figure 2. Period of greatest susceptibility to teratogenic effects (15).*

Preconception and gestational care are defined as a set of mediations that focus to describe and modify biomedical, behavioral, and social risk exposures to a woman's health or pregnancy outcome through prevention and management. Some steps should be taken before conception or early in pregnancy to have the largest repercussion on health results. Preconception care is more than a single visit to a health-care provider and less than all well-woman care, as defined by adding the full capacity of preventive and primary care services for women before a first pregnancy or between pregnancies (16).

Improving preconception health and pregnancy outcomes will require more than effective clinical care for women. Changes in the knowledge and attitudes and behaviors related to reproductive health among both men and women need to be made to improve preconception health. Despite several health promotion campaigns aimed at reducing smoking, misuse of alcohol, intimate partner violence, obesity and exposure to occupational hazards, the majority of adults are not aware of how these and other health and lifestyle factors influence reproductive health and childbearing (17)(18). Preconception health promotion, therefore, should focus on a general awareness among men and women regarding reproductive health and risks to childbearing (19).

### 1.3. ALCOHOL

Alcohol has an important role in our society, the intake of this liquid has a marked cultural and social well-established character. Unlike other drugs, alcohol can be consumed without necessarily involving health problems or addiction and this makes people not identify this product as a potential health risk. However, we know that globally alcohol is the 5th cause of disability and mortality (3.9% and 5.2% respectively of all deaths) in the world (20).

The scientific community has established parameters from which the intake of alcohol has an important impact on the health of individuals. Risk consumption is a pattern of alcohol consumption that increases the chances of adverse health effects if this type of consumption persists. The WHO establishes it from 20 grams per day of alcohol in women and from 40 grams per day in men (21).

Binge drinking is one of the most important concepts used in alcohol epidemiology to determine the burden resulting from alcohol use (22). In the 1990s, the term ‘binge drinking’ was introduced to describe a consumption pattern of a given amount of alcohol on a single occasion (23)(24). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) approved this definition of binge drinking as ‘a pattern of drinking

alcohol that brings blood alcohol concentration (BAC) to 0.08 grams percent or above. For the typical adult, this pattern corresponds to consuming 5 or more drinks (male), or 4 or more drinks (female), in about 2 hours' (25).

To determine the amount of alcohol ingested there are 2 types of measures:

a) The grams of alcohol consumed (gr). The alcohol content is expressed in degrees and measures the absolute alcohol content in 100 milliliters. Therefore, to calculate the content in grams of an alcoholic beverage we must multiply the degrees of it by the density of alcohol (0.8).

$$Grams\ of\ alcohol = \frac{Volume\ (mililiters) \times Alcohol\ content\ (proof) \times 0.8}{100}$$

b) Standard drinks units. It means the specific alcohol content of the different beverages.
According to the social characteristics of each country, the type of intake and the presentation of the product (can, bottle, cup...) grams may vary. In Spain a "drink unit" is equal to 10 grams of pure ethanol.

*Table 2. Alcoholic beverages and their standardization in grams and standard drink units.*

| | ALCOHOL GRAMS | STANDARD DRINK UNIT |
|---|---|---|
| 1 cup of wine or 1 glass of beer (200ml) | 10 grams | 1 unit |
| 1 liquor | 15 grams | 1.5 units |
| 1 spirit drink | 20 grams | 2 units |

## 1.4. PREGNANCY AND ALCOHOL CONSUMPTION

Alcohol use can result in harm not only to the drinker, but also to other individuals associated with the drinker. A classic example of this harm to others is the harm caused by consuming alcohol during pregnancy (26).

Globally, about 10% of women in the general population consume alcohol during pregnancy, and one of every 67 of these women delivered a child with fetal alcohol syndrome (FAS). It is also estimated that 4.3% of children born among heavy-drinking pregnant women (defined as an average of two or more drinks per day, or five to six drinks per occasion) will have FAS (26).

The prevalence of pregnant women who admit alcohol intake during gestation has been reported from 12% to 45% (27)(13).

In Murcia 72.3% of women consumed alcohol in the periconceptional period: 52% up to the 7th week of gestation, 26.3% up to the 9th week of gestation and 23.2% up to the 11th week of gestation (28).

In Málaga, a study was carried out through the implementation of a self-reporting questionnaire. A total of 451 women in the first, second or third trimesters of pregnancy were recruited. Consumption prevalences in each trimester were 40.7%, 25.5% and 17.1% (29).

In Catalonia, the only data we have about alcohol during pregnancy is from a study performed in Barcelona in a low socioeconomic status population, by determining fatty acids ethyl esters in meconium, this study found that 45% of mothers consumed alcohol during pregnancy (30).

We know the prevalence of alcohol consumption in Spain from the Spanish National Survey on Alcohol and other Drugs (EDADES). The survey has the collaboration of all the Autonomous Communities. This program is carried out every two years so that it is possible to observe the evolution of the prevalence of consumption of alcohol and other drugs (31).

The latest survey shows a regular or occasional global alcohol consumption of almost three quarters of women of childbearing age (Table 3) and almost one in 10 women has had binge-drinking in the last 30 days (Table 4) (31).

*Table 3. Prevalence (%) of any alcohol consumption among women of childbearing age in Spain by age range by 2017* (31).

| | 15-24 | 25-34 | 35-44 |
|---|---|---|---|
| Last 12 months | 72.8 | 72.1 | 69.2 |
| Last 30 days | 54.8 | 56.8 | 53.8 |
| Daily in the last 30 days | 0.7 | 1.2 | 2.4 |
| Never | 16.6 | 11.0 | 10.5 |

Comparing with previous editions of this survey (12), we could say that the alcohol intake in the last month of women at childbearing age has increased.

*Table 4. Prevalence of binge-drinking in the last month among women of childbearing age, by age range by 2017 (31).*

| | 15-24 | 25-34 | 35-44 |
|---|---|---|---|
| Binge-drinking in the last 30 days | 12.1 | 6.2 | 2.9 |

.

Pregnancy is a period in which the intake of alcohol is not as socially accepted as in other periods of life, although the population, in general, and health professionals, in particular, have not yet assumed a zero tolerance with alcohol during pregnancy (16).

Despite government campaigns (there is no safe level of alcohol) and that the most important health repercussions for the fetus are known by the population (32), it is striking that alcohol is one of the last actions that is carried out when planning pregnancy, since it is at the moment of diagnosis of pregnancy (at the end of early embryogenesis) the most common chosen moment to eliminate consumption.

Although the society is informed, it is not aware of the dramatic damages related to alcohol consumption in this period of life: it is the first preventable cause of mental retardation and congenital defects (33).

There are two ways to identify the use of illegal and legal drugs: through clinical interviews and through biological samples (34).

The clinical interview is a practical and inexpensive tool, the availability of data is immediate (time of consultation) and allows to make a timing of the exposures to which the pregnant woman has been subjected, the type and amount to which she has been exposed. The two most important drawbacks of this method are the memory bias and the possible lack of veracity both in the denial and in the quantity consumed. We must differentiate the clinical interview, conducted by trained and qualified professionals, from the self-filled questionnaire, in which it is the patient himself who fills in the data.

Biological Samples. The most common are urine, meconium and hair. Depending on the needs of the health professional/user each sample has advantages and disadvantages. Although there is no gold-standard test, urine is the most used because of its ease of collection. The biggest drawback of this method is that it only detects recent exposure. Meconium is also easy to collect and allows to identify exposures to illegal drugs in the 2nd and 3rd trimester, in contrast it is difficult to locate the time and amount to which the fetus was exposed and can also be contaminated by urine sample. Hair is easy to collect, and very long-term exposure can be detected from the time of consumption, using a ratio in which each centimeter of hair corresponds to one month of exposure, although time and quantity of exposure are difficult to determine. In addition, environmental pollution, hair type, sample volume and cosmetic processing of hair (dyes, highlights or discolorations) affect the interpretation of the results. It is the least used in clinical practice (35). Umbilical cord tissue toxicology testing yielded a similar detection rate compared to meconium testing. The use of umbilical cord tissue avoids detection of medications given to the neonate prior to meconium collection (36). A study was carried out in a low socio-economic area from Barcelona to disclose self-reporting through maternal hair analysis. In the self-reporting only 2.6% stated to have consumed alcohol on more than one occasion during pregnancy. Alcohol hair biomarkers showed that only 35.3% of women were totally abstinent during gestation, while 62.7% drank a non-negligible amount of alcohol during pregnancy, and 2% were chronic excessive drinkers. Based on these data we conclude that the self-reporting questionnaire is not useful for measuring the prevalence of alcohol consumption. The main disadvantage of meconium and umbilical cord tissue is that data is obtained retrospectively, so prevention and manage actions cannot be undertaken (37).

## 1.5. FETAL ALCOHOL SPECTRUM DISORDER

The consequences of prenatal alcohol exposure were first described more than 40 years ago, in 1973 (38)(39). The term “fetal alcohol syndrome” (FAS) was first used to describe the cluster of birth defects due to prenatal alcohol exposure (including growth restriction, craniofacial abnormalities and intellectual disabilities) with lifetime consequences. The term “fetal alcohol spectrum disorder” (FASD) has since been adopted to describe a broader spectrum of presentations and disabilities resulting from alcohol exposure in utero.

Alcohol use during pregnancy is an established cause of FASD, one of the most disabling potential outcomes of prenatal alcohol exposure. Despite the risk, a significant number of pregnancies are alcohol-exposed; it was recently estimated that in Canada, 10.0% of women consume alcohol while they are pregnant (26).

Alcohol use during pregnancy has been established as a risk factor for adverse pregnancy outcomes, including stillbirth (40), spontaneous abortion (41), premature birth (42)(43)(44); intrauterine growth retardation (44)(45); and low birth weight (46)(44).

The development of clinical capacity for FASD diagnosis remains difficult, because the diagnosis requires a medical evaluation and neurodevelopmental assessment conducted by a multidisciplinary team (47).

In 2005, an international, collaborative, evidence-based guideline for diagnoses related to prenatal alcohol exposure was published. As outlined in this guidelines for diagnosis, FASD includes the following three alcohol-related diagnoses: fetal alcohol syndrome (FAS), partial FAS (pFAS), and alcohol-related neurodevelopmental disorder (ARND) (48).

Since then, the field has evolved, and additional evidence, expertise and experience have emerged to suggest that a revision was required to improve both diagnoses and outcomes. The literature has also shown that impairments in behavior and function associated with FASD have been detected from exposure to binge drinking, even infrequently or early in pregnancy, which underscores the importance of pre-pregnancy counselling (47).

The guideline provides recommendations on the screening, referral and support for pregnant or postpartum women and for individuals at risk of FASD; the medical assessment, including family history, maternal alcohol history, physical examination

and differential diagnosis; the sentinel facial features; the neurodevelopmental assessment; the nomenclature and diagnostic criteria; and the diagnostic team and special considerations in the neurodevelopmental assessment of infants and young children (47). Different approaches to the diagnosis have been discussed, although the main features remain (49).The algorithm for diagnosis is reflected in Figure 3.

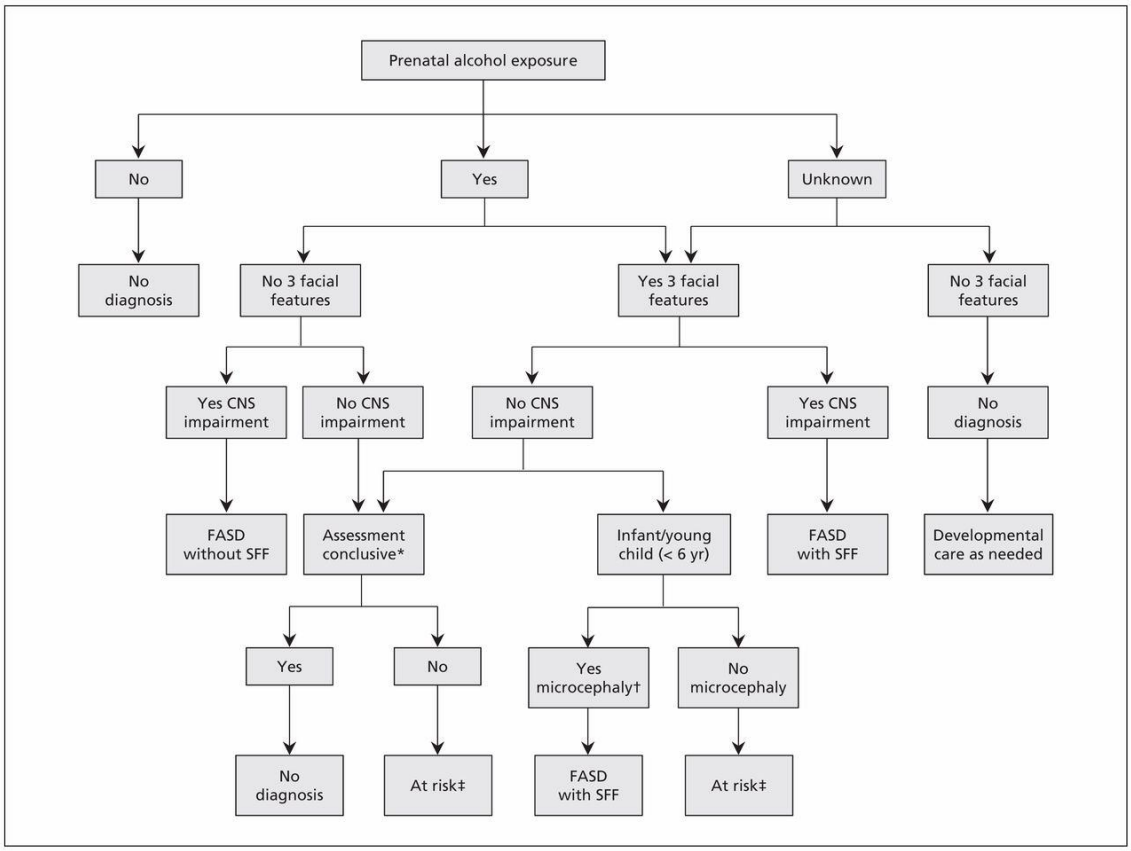


*Figure 3. Diagnostic algorithm for FASD. Assessment conclusive = clinician conducting the neurodevelopmental assessment is satisfied that the session was a true representation of the person's ability and that any deficits reported were not due to extenuating circumstances. Assessments may be inconclusive for children under six years of age, because some domains cannot be assessed with confidence until the person is older or because of other confounding factors, such as temporary life stress or illness; see the text for more information. †Microcephaly is not the only pathway to diagnosis for infants and young children; these individuals may also receive other FASD diagnoses, as specified elsewhere in the algorithm, if they show three areas of substantial impairment on neurodevelopmental tests. ‡At risk for neurodevelopmental disorder and FASD, associated with prenatal alcohol exposure. An at-risk designation includes situations where a full neurodevelopmental assessment is not conclusive because of age or situational factors; therefore, FASD may not be the diagnosis. Clinical judgment is recommended. Note: CNS = central nervous system (yes/no impairment in ≥ 3 brain domains), SFF = sentinel facial features (47)*

Full FAS is characterized by a triad of signs: 1) prenatal and/or postnatal growth restriction; 2) central nervous system dysfunction demonstrated by intellectual impairment and/or structural abnormalities, microcephaly, developmental delay and complex behavioral problems; and 3) characteristic facial anomalies, including short palpebral fissures, a flat philtrum and thin vermilion border of the upper lip (50)(48)(47)(51).

The main effect of prenatal alcohol exposure is permanent central nervous system damage, which can lead to a myriad of adverse developmental outcomes in exposed children. Developing brain cells and structures can be malformed or have their development interrupted upon exposure to alcohol prenatally. Thus, FASD is associated with a wide range of effects, including permanent brain damage, congenital anomalies, prenatal and/or postnatal growth restriction and characteristic dysmorphic facial features, along with cognitive, behavioral, emotional and adaptive functioning deficits (48).

The clinical manifestations of FASD may include visual and hearing deficits, mental and behavioral disorders, language disorders, cardiac anomalies, urogenital defects and skeletal abnormalities (52).

FASD are a collection of physical, neurological, and behavioral conditions resulting from prenatal alcohol exposure. The prevalence of FASD varies among communities based on alcohol consumption patterns, birth control use, and occurrence of modifying factors (53).

Prevention of FASD may be approached in a number of ways: increasing awareness and knowledge of FASDs, decreasing alcohol consumption in pregnancy, reducing risky drinking prior to pregnancy and prior to recognition of pregnancy, and increasing the use of effective contraception (54).

Women of childbearing age who engage in risky drinking without effective contraception are at risk for having an alcohol-exposed pregnancy (AEP) and, as a result, a child with an FASD (54).

The precise risk of an AEP resulting in a child with an FASD is complicated by myriad maternal and fetal factors including the pattern of maternal alcohol consumption, maternal comorbidities and nutritional status, and maternal and fetal genetics (55)(56)(57)(58)(59)(60)(61).

In addition, FASD may be missed as a diagnosis for a variety of reasons, including lack of availability of accurate data on prenatal alcohol exposure. However, from the standpoint of prevention of FASD, the optimum goal is prevention of an AEP as there is no known safe amount of alcohol to consume in pregnancy (54).

The goal of the intervention modified to incorporate motivational interviewing was to decrease risky drinking in nonpregnant women with primary motivation being the well-being of a future baby (54).

Cultural factors influence the efficacy of interventions. Tailoring assessment tools (62) and interventions to a specific population have been found to be meaningful (63)(64).

The neurodevelopmental impairments associated with FASD can, later in life, lead to other common adverse outcomes, such as academic failure, substance abuse, mental health problems, contact with law enforcement and an inability to live independently and obtain and maintain employment (65).

### 1.6. FAS PREVALENCE

To set priorities for public health policy, funding for public health initiatives, and health-care planning, it is necessary to know the prevalence of FAS and its main causal risk factor—alcohol use during pregnancy. However, to date, most countries do not have prevalence data at a population level for alcohol use during pregnancy or for FAS. Furthermore, to the best of our knowledge, the number of pregnant women in the general population who consume alcohol during pregnancy per case of FAS has not been previously estimated (26).

Although human research has not been able to delineate the pattern, amount, or critical period of prenatal alcohol exposure necessary for structural or functional teratogenesis, we do know that not every woman who drinks during pregnancy will deliver a child with FAS. This uncertainty is especially true given that there are some other factors at play that might influence a fetus's vulnerability to the teratogenic effects of alcohol, such as variability in the metabolism and genetic background of both the mother and fetus, environmental influences, maternal smoking behavior, nutritional status, stress levels(66)(67), and possibly paternal lifestyle (68).

To fill these knowledge gaps, a study aimed to estimate the prevalence of alcohol use during pregnancy and of FAS among the general population, by country, WHO region (ie, African region [AFR], Eastern Mediterranean region [EMR], European region

[EUR], region of the Americas [AMR], South-East Asia region [SEAR], and Western Pacific region [WPR]), and globally. It also aimed to estimate the number of pregnant women in the general population who consumed alcohol per one case of FAS by linking data on the prevalence of alcohol use during pregnancy with data on the prevalence of FAS. (26)

*Table 5. Global prevalence of alcohol use (any amount) during pregnancy and FAS in the general population in 2012, by WHO region* (26).

| | Alcohol use during pregnancy | FAS (per 10000) |
|---|---|---|
| AFR | 10% | 14.8 |
| AMR | 11.2% | 16.6 |
| EMR | 0.2% | 0.2 |
| EUR | 25.2% | 37.4 |
| SEAR | 1.8% | 2.7 |
| WPR | 8.6% | 12.7 |
| Worlwide | 9.8% | 14.6 |

In 2017 a global review of FASD and alcohol intake prevalences was published and reported unacceptably high global prevalence rates of alcohol use in pregnancy (9.8%) and fetal alcohol syndrome (FAS) (14.6 cases per 10 000 population) and estimate that one in every 67 women who consumed alcohol during pregnancy would deliver a child with FAS, which translates to about 119 000 children born with FAS in the world every year (26). Globally, the proportion of FAS cases among all FASD cases was recently estimated to be 18.9%; that is, approximately two out of 10 people with FASD will be diagnosed with FAS (26). This finding is tragic because FAS is leading cause of intellectual disability, birth defects, and developmental disorders, yet is entirely preventable (69).

FAS is a lifelong condition which might also result in secondary disabilities including academic failure, substance misuse, mental ill-health, and contact with the law due to illegal behaviors, with huge resultant costs to our health, education and justice sectors (70)(26).

The average prevalence of alcohol use during pregnancy was the highest in the WHO EUR at 25.2%. In line with the prevalence of alcohol use during pregnancy, the prevalence of FAS was the highest in WHO EUR (37.4 per 10 000 people) (26).

The prevalence of alcohol use during pregnancy and FASD prevalence in Catalonia is unknown. The only data we have about alcohol intake during pregnancy is from the Murcia Region (28).

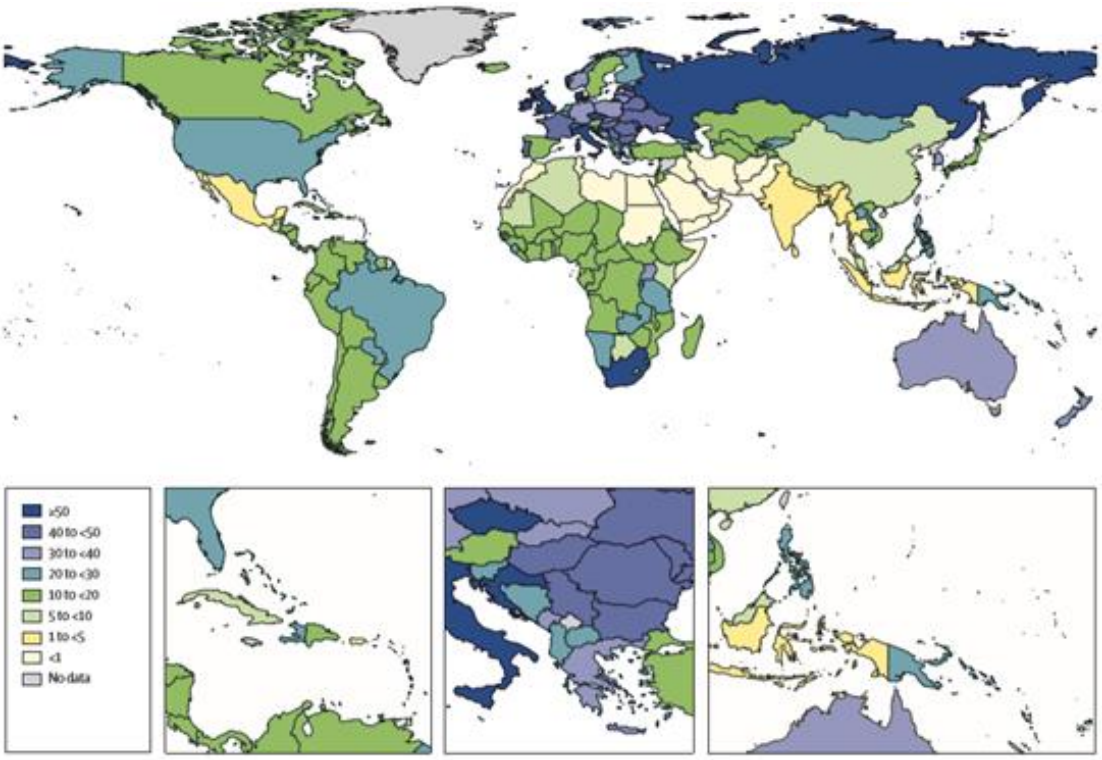


*Figure 4. Global prevalence (%) of alcohol use (any amount) during pregnancy among the general population in 2012* (26).

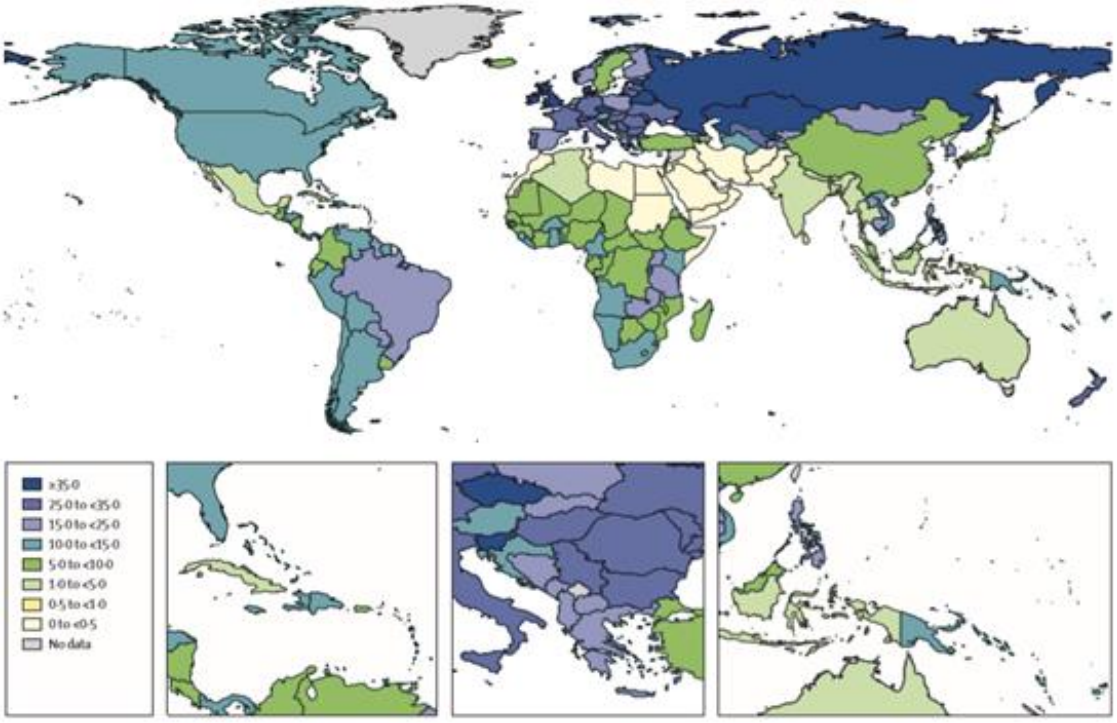


*Figure 5. Global prevalence (per 10 000 people) of FAS among the general population in 2012* (26).

FASD might be 10-15 times more prevalent among foster/adopted children compared to the general population; however, many of these children remain undiagnosed or misdiagnosed. The lack of confirmed prenatal alcohol exposure (PAE) may be a key barrier to diagnosis (71).

Information on prevalence of special needs in internationally adopted children (IAC) is incomplete. An Italian study reviewed data from 422 IAC screened at a single Centre in Italy in 2015-16. Prevalence of special needs reached 17.1%. Among these children, the most frequent conditions were fetal alcohol spectrum disorders (FASD; 7.1%), cleft lip palate (1.9%) and other congenital malformations (4.7%). Worrisomely, 25 out of 52 (48.1%) Russian children presented with FASD (72).A recent study describes the neuropsychological profiles of a group of internationally adopted children in Catalonia from China, Russia, Colombia and Ethiopia. During the last years, International adoption has increased significantly in our country over the last few years. China, Russia, Colombia and Ethiopia represent 77% of international adoptions in Spain. In Catalonia, children adopted from Russia and other eastern Europe countries have greater neuropsychological difficulties than the others (73). Most pre-adoption history is unknown; therefore, we are unable to determine the origin of these difficulties, although some could fit a FASD diagnosis even if prenatal alcohol exposure is unknown (see Figure 3). Maternal alcohol consumption during pregnancy and the institutional environment could be influencing factors in neuropsychological delay (73).

Despite public health efforts to eliminate or reduce the consumption of alcohol during pregnancy in many countries, the results of the current studies indicate that in some regions (most notably, WHO EUR), a high number of pregnant women continue to consume alcohol. Alarmingly, about a quarter of women in the general population of Europe drink alcohol during pregnancy, which, as one would expect, is mirrored by also having the highest FAS prevalence—a prevalence that is 2.6 times higher than the global average (26).

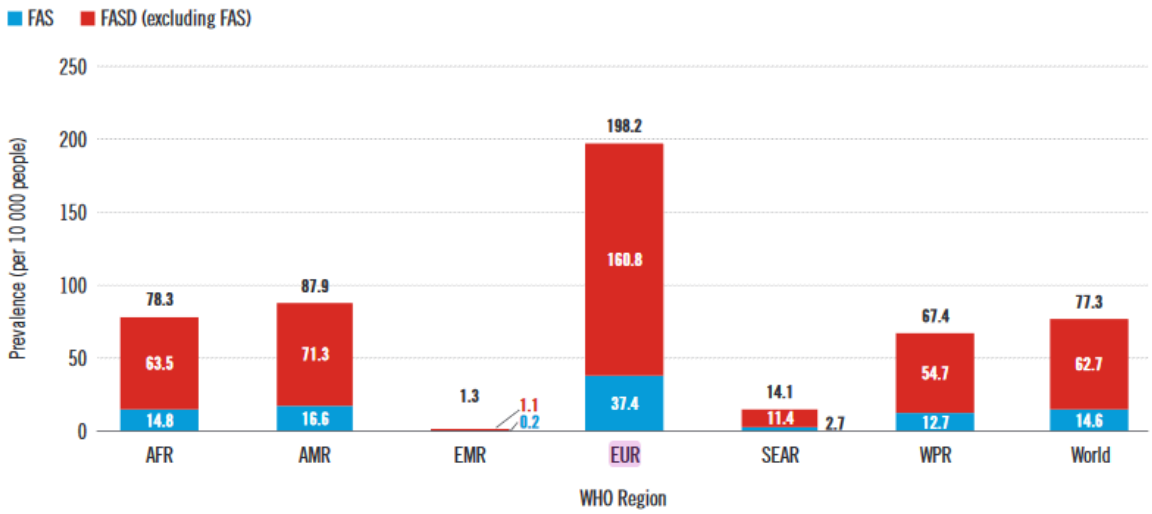


*Figure 6. Prevalence of fetal alcohol syndrome and fetal alcohol spectrum disorders in the general population, by WHO region* (22).

The lowest prevalence of alcohol use during pregnancy and FAS was found in the WHO EMR (50 times lower than the global average) and WHO SEAR (five times lower than the global average). This is unsurprising given the cultural factors in these regions, which prescribe female abstinence (26).

It is believed that the prevalence ratio of FAS to FASD is about one to nine or ten, indicating that FAS is only the tip of the iceberg (74).

In addition, the estimates presented in this report are for the general population of the respective countries. However, the prevalence of alcohol use during pregnancy has been reported to be much higher among some at-risk populations (26).

Regardless of the preventable nature of FAS, there is reason to believe that its prevalence could increase around the globe in the coming years. This speculation is primarily based on two factors: first, the rates of alcohol use, binge drinking, and drinking during pregnancy are increasing among young women in a number of countries (20), and second, a large percentage of pregnancies in developing and developed countries are unplanned (75)(76)(77)(78).

(79)(80).

Appropriate screening for alcohol use in all women of childbearing age in combination with preconception health promotion, contraceptive counselling, and referral to substance abuse programs for those women identified to have an alcohol use disorder should become a routine standard of care in all primary care settings. Referrals to substance abuse programs, if necessary, are of the utmost importance as effective

treatment of any identified cases of alcohol dependence or alcohol use disorders could reduce the risk of having a child with FAS. In patients in whom it is not possible to detect alcohol use before pregnancy, detection of prenatal alcohol use should be the focus, as decreasing or eliminating the use of alcohol during pregnancy could reduce the severity of the effects on the fetus. As the first point of contact, physicians and other health-care providers are in a position to fulfil a crucial role in the primary prevention of FAS and other alcohol-related birth defects (26).

### 1.7. FAS COSTS

The costs totaled approximately 1.8 billion Canadian dollars (CAD) (from about 1.3 billion CAD as the lower estimate up to 2.3 billion CAD as the upper estimate). The highest contributor to the overall FASD-attributable cost was the cost of productivity losses due to morbidity and premature mortality, which accounted for 41% of the overall cost. The second highest contributor to the total cost was the cost of corrections, accounting for 29%. The third highest contributor was the cost of health care at 10% (70). We could say that FASD is a significant public health and social problem that consumes resources, both economic and societal. Many of the costs could be reduced with the implementation of effective social policies and intervention programs. (70).

Emphasizing the economic burden of FASD, it has been shown that the highest rate of economic returns comes from the earliest investments in children, providing an eye-opening understanding that society invests too much money on later development when it is often too late to provide great value (see figure 7). This Heckman curve shows the economic benefits of investing early and building skill upon skill to provide greater success to more children and greater productivity and reduce social spending for society. (81)

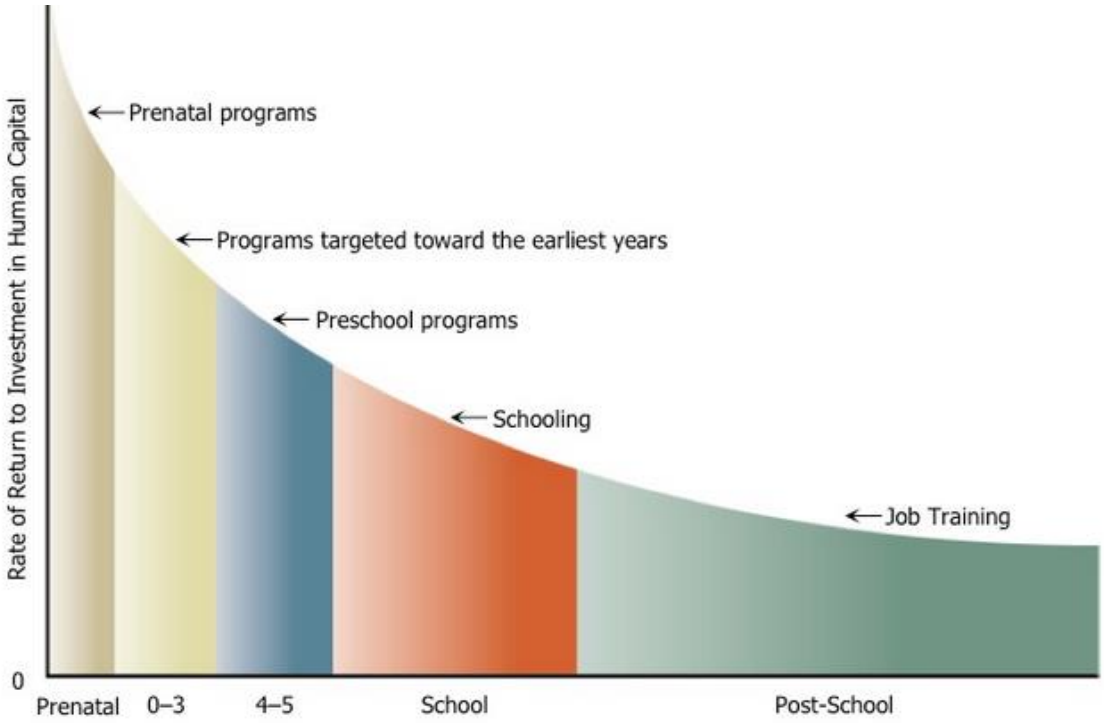


*Figure 7. The Hecknam curve* (81).

### 1.8. COUPLE ROLE

Historically, men have not considered that the exposures to which they may be subjected during pregnancy or the periconceptional period (spermatogenesis) may be a risk to their future child. The man, due to his education and biological characteristics (he is not pregnant, nor does he have physical/emotional/hormonal changes) assumes his paternal role later than the woman. In most cases, they fully assume this function from the time of delivery.

The man and/or couple has 4 fundamental roles in pregnancy (biological, behavioral model, environment creator and psychosocial):

#### 1.8.1. BIOLOGICAL ROLE

It is currently known that in the period of spermatogenesis (approximately 70 days before conception) the future father is creating the genetic material that will be inherited to his future son (50%). At this moment the level of divisions of the genetic material is very important and becomes a critical period and very vulnerable to exposure to certain environmental toxics (toxic habits, hobbies related to the use of chemicals such as paints, solvents, gasoline or domestic and occupational exposures)(82).

Recent findings have sparked interest in epigenetic alterations of paternal genomes and its effects on offspring. This emergent field focuses on how environmental influences can epigenetically alter gene expression and ultimately change the phenotype and behavior of progeny (68). Some studies on various contaminants, nutrition, and lifestyle-related conditions suggest a paternal influence on the offspring's future health. Inclusion of paternal factors in future research will ultimately improve the understanding of transgenerational epigenetic plasticity and health-related effects in future generations (83)(84)(85)(86).

### 1.8.2. BEHAVIOR MODELS

Once conception takes place, the man/partner acquires an inducing role with the life habits he has. They are small actions such as quitting smoking, eliminating illegal drugs and alcohol ... which provides stability to the ecosystem of women reducing their stress and anxiety (87).

For example, it is important to consider the correlation between paternal and maternal alcohol intake. If the father does not drink alcohol, not only does the semen quality increase but it also helps the mother to keep away from drinking during pregnancy. In regard to alcohol intake, we need to take a comprehensive and family approach (28).

## 2. JUSTIFICATION

There are no data on prenatal exposure to alcohol in Catalonia (only those from the EDADES surveys and some specific study of the population with a low socioeconomic level).

There is no specific data on how many children may be affected (we have global data, EUR). Currently in the region of La Garrotxa there is no diagnosis of FASD, although statistical data tell us that there is an alcohol intake that affects the fetus.

The introduction of a screening tool to quantify alcohol consumption in pregnant couples is a very useful method not only to quantify the consumption of alcohol that may affect the fetus, but also to diagnose whether the future newborn could be affected by a disorder related to alcohol exposure.

This study is performed at the Pediatric Environmental Health Specialty Unit (PEHSU) of La Garrotxa. The PEHSU Garrotxa, is the first unit of these characteristics in all of Catalonia and the second in operation throughout the State, where PEHSU Murcia is also found.

## 3. RESEARCH HYPOTHESIS

Our hypothesis is that specific screening for prenatal exposure to alcohol will detect a higher level of consumption than that recorded before it was implanted, that it can detect a population at risk and that their mere implantation will have reduced the consumption of alcohol.

## 4. OBJECTIVES

### 4.1. PRIMARY OBJECTIVES

-To quantify the prenatal exposure to alcohol in the region of La Garrotxa.

-To determine the frequency of embryos/fetuses at high risk of developing FASD.

### 4.2. SECONDARY OBJECTIVES

- To estimate the effect of a specific prenatal screening program for alcohol on the consumption of pregnant couples over 3 years.

# 5. METHODS

## 5.1. TRIAL DESIGN

Clinical, observational, longitudinal and descriptive study to evaluate prenatal alcohol exposure in pregnant couples during her first in the pregnancy follow-up and control program.

## 5.2. STUDY POPULATION AND RECRUITMENT

The target population were pregnant women and their partners, whose reference unit was Garrotxa Pediatric Environmental Health Specialty Unit of the Hospital d'Olot i Comarcal de La Garrotxa in Olot (Garrotxa county).

Future parents were identified during their first visit to the Obstetrics Department (gynecologists or midwives) during first trimester of pregnancy and invited to participate in the study.

The sample was collected between October 2016 and December 2018.

The pregnant couples were transferred by the midwives, obstetricians and general practitioners to the Pediatric Environmental Health Specialty Unit of La Garrotxa as a part of the regular pregnancy program of the Garrotxa county.

Garrotxa is a comarca (county) in Girona, Catalonia, Spain. Its population in 2016 was 55,999, more than half of them in the capital city of Olot. The paediatric population is 8000 children and the birth rate is 400 births per year (88).

The health areas (ABS) that belong to the PEHSU of this hospital are the following:

-ABS Olot;
-ABS Olot Nord;
-ABS Besalú;
-ABS Vall d'en Bas–Hostoles (CAP St. Esteve d'en Bas; CL St. Feliu de Pallerols; CL Les Planes d'Hostoles; CL St. Privat d'en Bas; CL Riudaura);
-ABS Sant Joan (CAP St. Joan les Fonts; CL Castellfollit de la Roca; CL Vall de Bianya-La Canya).

### 5.2.1. Inclusion criteria:

All pregnant women and their partners who participated in the prenatal consultation in the Hospital d'Olot i Comarcal de La Garrotxa.

### 5.2.2. Exclusion criteria:

None.

## 5.3. SAMPLE SIZE AND SAMPLING

Sample size: our sample consists on 616. With this sample size, prevalences of alcohol exposure between 10% and 40% can be estimated with a 95% confidence and a precision of 5 percent units (https://www.imim.cat/ofertadeserveis/software-public/granmo/).

Sampling: no probabilistic. Subjects were recruited among those seeking attention at our center.

## 5.4. VARIABLES:

### 5.4.1. MAIN VARIABLES:

- Periconceptional maternal alcohol consumption: this variable corresponds to maternal alcohol consumption during the periconceptional period, which refers to the period from 3 months before pregnancy to the time of conception, which can be calculated through the date of last menstruation.
- Current maternal alcohol consumption: this variable corresponds to the woman's alcohol consumption at the time of the interview, that is, once she was aware of the pregnancy diagnosis.
- Binge-drinking maternal episodes during pregnancy: this variable corresponds to maternal binge-drinking episodes during pregnancy. Binge-drinking is defined as a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 grams percent or above. For the typical adult, this pattern corresponds to consuming 5 or more drinks (male), or 4 or more drinks (female), in about 2 hours.

### 5.4.2. SECONDARY VARIABLES:

- Maternal ethnicity: by ethnicity we mean a category of people who identify with each other based on similarities such as common ancestry, language, history, society, culture or nation. The ethnic groups included in this study are shown in the table 6.
- Paternal ethnicity: by ethnicity we mean a category of people who identify with each other based on similarities such as common ancestry,

language, history, society, culture or nation. The ethnic groups included in this study are shown in the table 6.

*Table 6. Ethnicity categories.*

| Ethnicity categories |
|---|
| Arabic/North African |
| White/Caucasian |
| Gypsy |
| Indian/Pakistani |
| Latin American |
| Black/Sub-Saharan/Caribbean |
| South East Asia/Chinese |

- Partner's education level: this variable refers to the level of education of the mother partner. All possible levels included in this study are shown in the following table.
- Maternal education level: this variable refers to the level of education of the mother. All possible levels included in this study are shown in the following table.

*Table 7. Educational levels.*

| Educational level categories |
|---|
| High school |
| Vocational training |
| Primary school |
| Junior high school |
| Unschooled |
| University |

- Cessation time: this variable refers to the week of gestation in which pregnant women who drank in the periconceptional period stopped drinking. Includes values from gestation week 0 to gestation week 42.
- Alcohol exposure during spermatogenesis: this variable refers to the consumption of alcohol by the father during spermatogenesis, that is, from 70 days before conception to the time of intercourse.
- Family net income per month (€): this variable refers to the total amount of net money the household receives each month. All the options contemplated in this study are shown in the following table (table 8).

*Table 8. Family net income per month in EUROS.*

| Family net income per month (€) |
|---|
| <800€ |
| 800-1500€ |
| 1500-2000€ |
| 2000-2500€ |
| 2500-3500€ |
| >3500€ |

- Mother's age.
- Partner's age.

All these variables, both primary and secondary, have been measured by means of the GP (see exposure data: Green Page).

### 5.5. EXPOSURE DATA: GREEN PAGE

The prenatal alcohol exposure was evaluated through the Green Page (GP) Questionnaire. The GP is a set of basic and concise questions that allows us to detect, inform and reduce/eliminate the environmental risk factors from the periconceptional stage, during pregnancy, lactation and the breeding period, contributing to the creation of healthier environments for children (89). This GP was first created and implanted in the Paediatric Environmental Health Speciality Unit (PEHSU) Murcia and has been used for many years (90) and has been awarded as a Good Practice by the Spanish Ministry of Health (91) .

The sections included in the GP are: socioeconomic status, obstetrical-reproductive antecedents, ionizing radiation, pharmacy (includes parapharmacy, homeopathy and vitamin supplements), occupational exposures, hobbies of chemical risk, legal and illegal drugs, home, pesticide exposures intra/extra home and environmental risk perception of parents in the home and community. The GP used is shown in Annex 1. The exposure to ethanol was explored from the periconceptional stage to the moment of interview (Table 9). This table allowed the conversion of alcohol consumption to grams per day during critical periods (periconceptionally, weeks 3–5, weeks 6–7, and weeks 8–10 of embryonic development). We assumed that the alcohol content for each type of drink (wine or beer) was equivalent to 10 g of alcohol. The data were obtained through a face-to-face interview by two different specifically-trained health providers.

| | Never <1 month | 1-3 per month | 1 per week | 2-4 per week | 5-6 per week | 1 per day | 2-3 per day | 4-5 per day | ≥ 6 per day | Grams per day |
|---|---|---|---|---|---|---|---|---|---|---|
| Red, pink or white wine; vermouth (1 glass, 4 oz.) (10 g/alcohol) | 0 | 0.6 | 1.42 | 4.28 | 7.85 | 10 | 25 | 45 | 60 | A |
| Beer (1 can or 1/5 bottle, 8 oz) (10g/alcohol) | 0 | 0.6 | 1.42 | 4.28 | 7.85 | 10 | 25 | 45 | 60 | B |
| Liquor (20-30º proof); fruit; herbs; whiskey cream (1 glass, 2 oz.) (15g/alcohol) | 0 | 0.75 | 2.1 | 6.43 | 11.78 | 15 | 37.5 | 67.5 | 90 | C |
| Alcohol (>30º proof): brandy; gin; rum; whiskey; vodka (1 glass, 2 oz.) (20g/alcohol) | 0 | 1.2 | 2.84 | 8.56 | 15.7 | 20 | 50 | 90 | 120 | D |
| Alcohol-free beer (1 can or 1/5 bottle, 8 oz) (2/alcohol) | 0 | 0.13 | 0.28 | 0.85 | 1.57 | 2 | 5 | 9 | 12 | E |
| A+B+C+D+E = TOTAL GRAMS OF ALCOHOL PER DAY | | | | | | | | | | |

*Table 9. Checklist to quantify the grams of alcohol consume (grams/day).*

## 6. STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc, Chicago, Illinois). Results for variables with a normal distribution were expressed as mean and standard deviation, and those for variables without a normal distribution were expressed as median and interquartile range. Nonparametric variables were mathematically transformed to improve symmetry. Frequencies (n) and percentages for each category were used to describe categorical variables.

## 7. ETHICAL CONSIDERATIONS

This project has been made according to the ethical considerations and requirements set out for international and national standards for epidemiological studies.

The four ethical principles of respect, justice, no maleficence and beneficence have been followed, established by the World Medical Association (WMA) in the *Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects* and in the *Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks.* The study was also submitted to the "Comité de Ética de Investigación Clínica (CEIC) del Hospital Universitario Doctor Josep Trueta", who accepted it in order to allow the development of the study. The Hospital's Ethics Committee and the Institutional Review Board approved the survey.

All personal and clinical information within this study will remain confidential and only used for research purposes according to the "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos y Garantía de los Derechos Digitales".* In order to ensure human dignity and human rights, among many others, "*Ley 14/2007, de 3 de julio, de Investigación Biomédica"* was also strictly respected.

All the patients were provided with all the information and document needed, as well as the written informed consent (view annex 2), which had to be signed. The investigators made sure that the patient understood all the information before signing it.

Content, of the database remained encrypted and the patient's identities confidential. All data have been treated without identification information.

## 8. RESULTS AND DISCUSSION

A total of 616 pregnant couples were recruited, with an increasing number of couples each year (Figure 8). Although the number of couples interviewed per year has increased, there has been a decrease in alcohol consumption. Sociodemographic data is shown in Table 10.

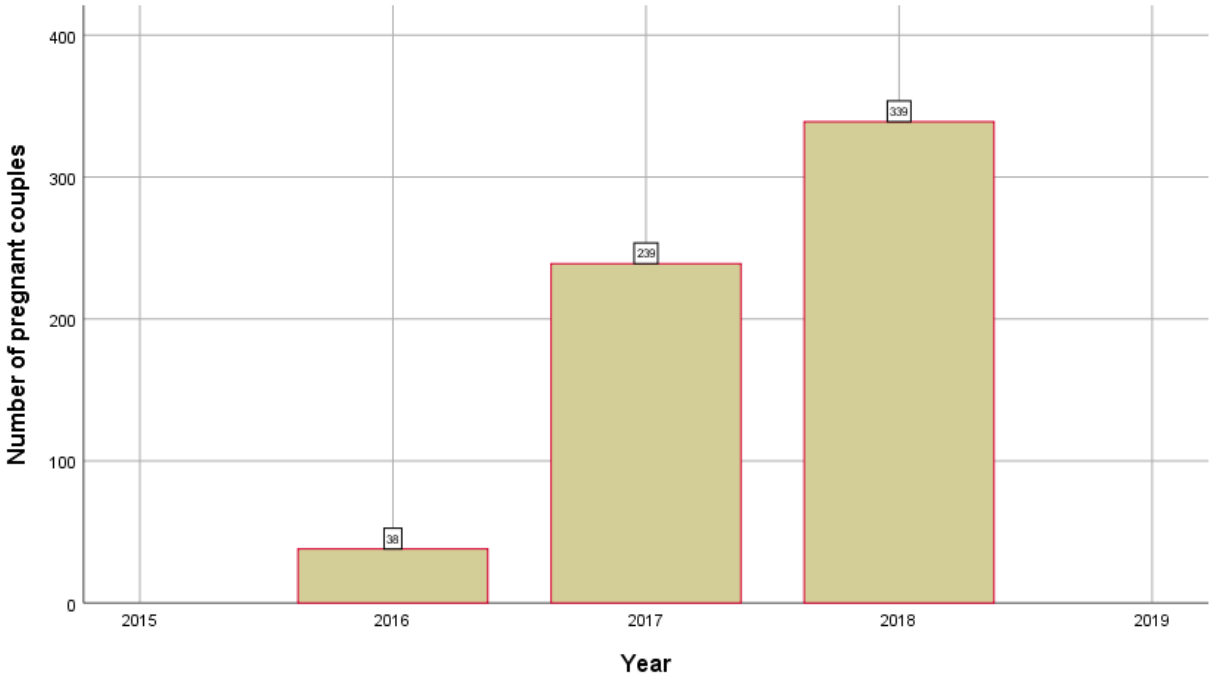


*Figure 8. Number of pregnant couples per year.*

*Table 10. Sociodemographic data.*

| | Number | Frequency (%) | Mean (CI 95%) |
|---|---|---|---|
| Pregnant's age | | | 31,2 (30,8 – 31,6) |
| Partner's age | | | 35,0 (34,4 – 35,5) |
| Mother's ethnicity | | | |
| Arabic/North African | 56 | 9,1 | |
| White/Caucasian | 408 | 66,2 | |
| Gypsy | 2 | ,3 | |
| Indian/Pakistani | 52 | 8,4 | |
| Latin American | 66 | 10,7 | |
| Black/Sub-Saharan/Caribbean | 18 | 2,9 | |
| South East Asia/Chinese | 11 | 1,8 | |
| Partner's ethnicity | | | |
| Arabic/North African | 61 | 9,9 | |
| White/Caucasian | 406 | 65,9 | |
| Gypsy | 2 | ,3 | |
| Indian/Pakistani | 53 | 8,6 | |
| Latin American | 53 | 8,6 | |
| Black/Sub-Saharan/Caribbean | 19 | 3,1 | |
| South East Asia/Chinese | 9 | 1,5 | |
| Pregnant's educational level | | | |
| High school | 63 | 10,2 | |
| Vocational training | 139 | 22,6 | |
| Primary school | 56 | 9,1 | |
| Junior high school | 123 | 20,0 | |
| Unschooled | 10 | 1,6 | |
| University | 223 | 36,2 | |
| Partner's educational level | | | |
| High school | 75 | 12,2 | |
| Vocational training | 159 | 25,8 | |
| Primary school | 88 | 14,3 | |
| Junior high school | 148 | 24,0 | |
| Unschooled | 14 | 2,3 | |
| University | 122 | 19,8 | |
| Family net income per month (€) | | | |
| <800€ | 36 | 5,8 | |
| 800-1500€ | 176 | 28,6 | |
| 1500-2000€ | 114 | 18,5 | |
| 2000-2500€ | 134 | 21,8 | |
| 2500-3500€ | 120 | 19,5 | |
| >3500€ | 34 | 5,5 | |

Along the total period of the study, a 54,8% drank some number of alcoholic beverages during the periconceptional time. Thus, less than the half of our sample were abstemious that time. Those who drank, 14,9% quit drinking before the day of last menstrual period, but 84,7% quit drinking during pregnancy, and it occurred mostly during the 5$^{th}$ week of gestation (mean 5,3, CI 95% 4,9-5,7, minimum 0 maximum 25) (Figure 9). Only 0,5% remained to drink during the whole pregnancy.

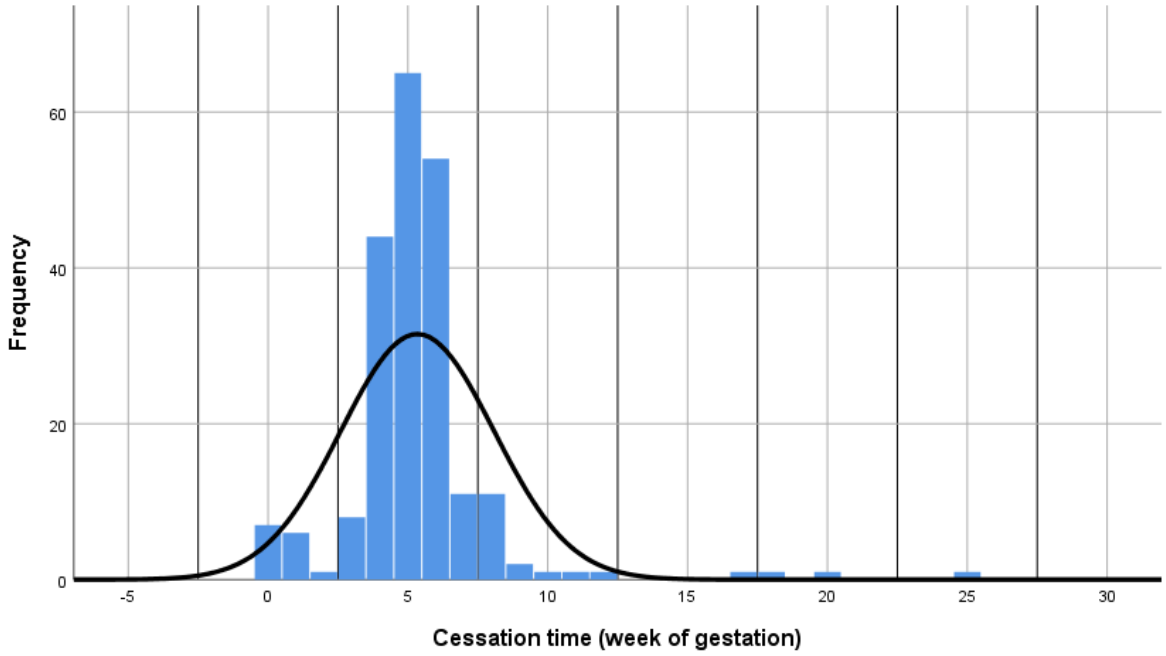


*Figure 9. Frequency of alcohol consumption and cessation time.*

A scatterplot was made to see if there was a correlation between two variables, the amount of alcohol consumption during the periconceptional period and the week of gestation in which they gave up the habit of drinking alcohol. As we see in the following figure (figure 10), there is no positive or negative correlation between these two variables.

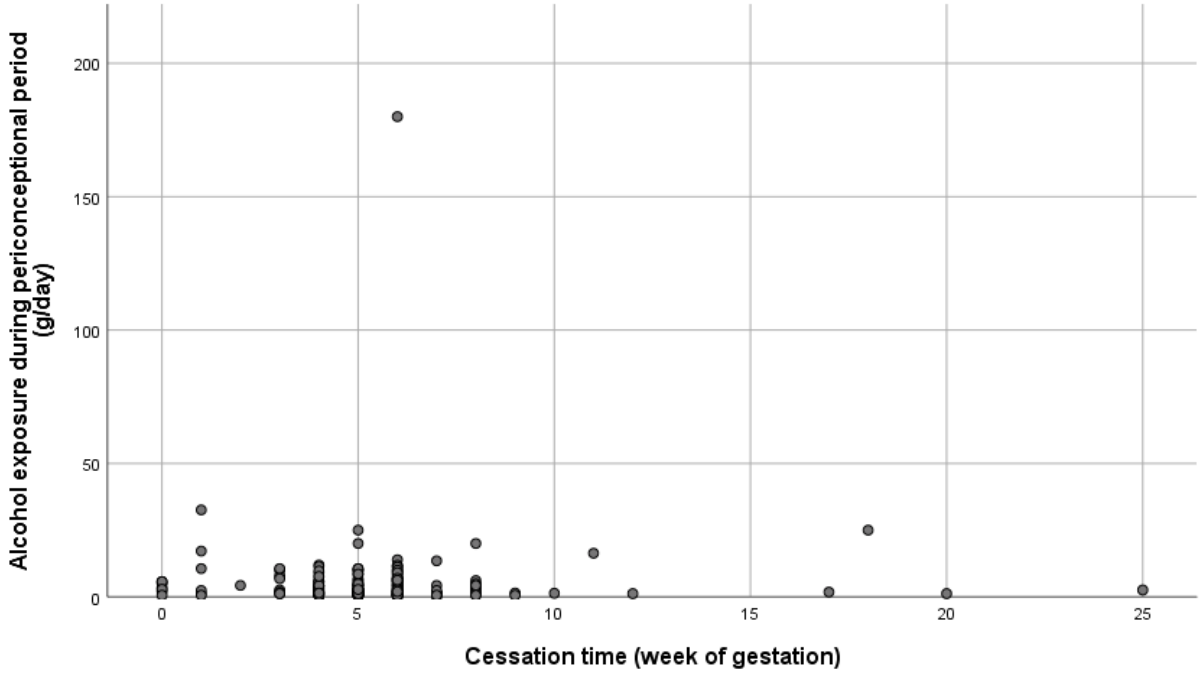


*Figure 10. Periconceptional alcohol and time of cessation*

For those pregnant women who drank any amount of alcohol, most of them had little amounts (18,7% drank less than 1g/day and 72,7% drank less than 5g/day). A 13,9% drank more than 6 drinks per week, and 2,7% had ≥20g/day (1,2% of the total of pregnant women).

For those who kept drinking, 89,0% drank less than 1g/day, and only 1,8% drank more than 5g/day. Only one pregnant woman kept drinking more than 6 drinks per week and one drank more than 20g/day.

Most of pregnant women (81,3%) did not experienced a binge drinking episode. 2% of the women had 2 or more binge-drinking episodes and 1,4% had ≥3 episodes.

During spermatogenesis, the mean of alcohol consumption in men was 7,2 g/day (CI 95% 6,3-8,2). Almost a third (27,9%) did not drink during that period. Of the whole, 10% drank ≥20g/day and 2,7% of men had a risk alcohol habit (≥40g/day).

Percentiles of alcohol exposure are shown in Table 11.

*Table 11. Percentiles of alcohol exposures.*

| Percentiles | 50 | 75 | 95 |
|---|---|---|---|
| Maternal alcohol exposure during periconceptional period (g/day) | 0,6 | 2,4 | 10,0 |
| Maternal alcohol exposure at the interview moment (g/day) | 0,0 | 0,0 | 0,6 |
| Maternal binge-drinking episodes | 0 | 0 | 1 |
| Alcohol exposure during spermatogenesis (g/day) | 2,8 | 9,9 | 28,5 |

A total of 2,4% of the embryos/fetuses were at high risk of developing FASD (≥20g/day and/or ≥3 binge drinking episodes), but in a less restrictive criteria (>6 drinks/week and/or ≥2 binge drinking episodes) this would rise to 5,8%.

The whole consumption of alcohol for both pregnant women and couples decreased during the period of study (Table 12), and we found a reduction of alcohol exposure (Figure 11).

*Table 12. Mean alcohol exposure along the period.*

| Year | | Maternal periconceptional alcohol consumption | Current maternal alcohol consumption | Maternal binge-drinking episodes | Alcohol exposure during spermatogenesis |
|---|---|---|---|---|---|
| 2016 | Mean (gr) | 4,76 | 1,09 | 0,79 | 17,31 |
| | N | 30 | 31 | 29 | 30 |
| | Variance | 7,59 | 5,25 | 2,27 | 24,33 |
| 2017 | Mean (gr) | 3,12 | 0,09 | 0,45 | 6,73 |
| | N | 237 | 233 | 225 | 227 |
| | Variance | 12,37 | 0,37 | 1,49 | 10,08 |
| 2018 | Mean (gr) | 2,02 | 0,11 | 0,19 | 6,96 |
| | N | 335 | 337 | 334 | 305 |
| | Variance | 3,41 | 0,57 | 0,52 | 10,58 |
| Total | Mean (gr) | 2,59 | 0,15 | 0,32 | 7,42 |
| | N | 602 | 601 | 588 | 562 |
| | Variance | 8,36 | 1,29 | 1,13 | 11,74 |

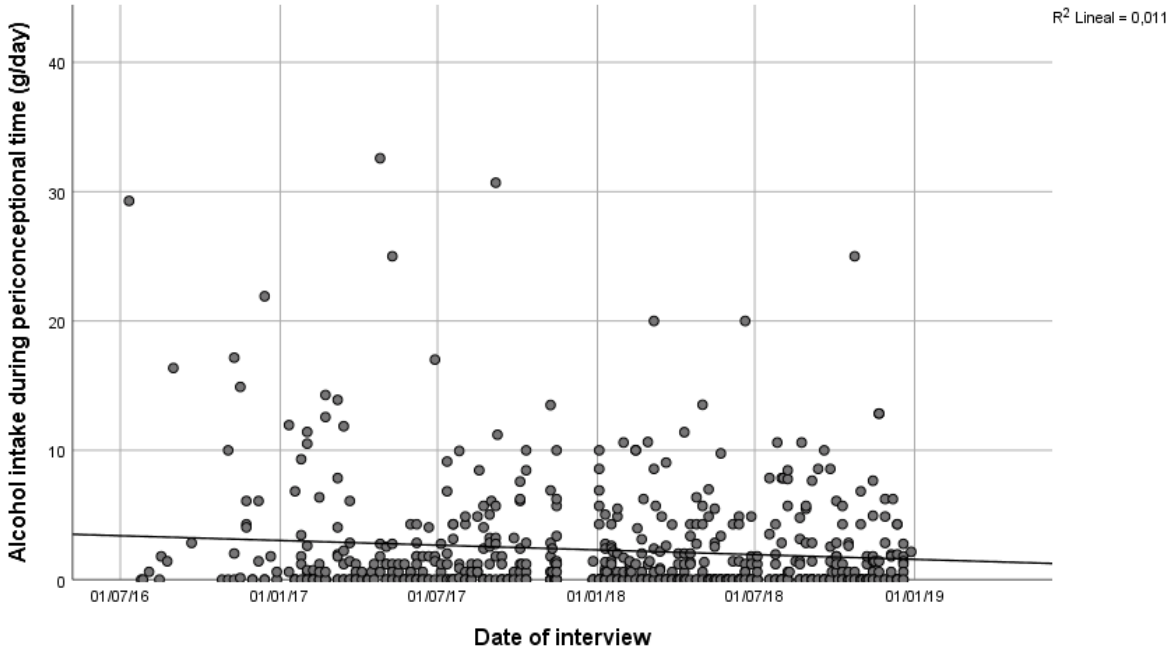


*Figure 11. Evolution of alcohol exposure in periconceptional time.*

Alcohol during pregnancy has a low risk perception by the general population and is under-diagnosed by health professionals. One of the greatest problems when diagnosing developmental alterations caused by alcohol exposure in children is that it is much more frequent alterations at the level of neurodevelopment, which are

noticeable only after the first years of life of the child, and once identified the damage, the time elapsed from pregnancy to diagnosis makes the hypothesis of damage by alcohol intake lose force.

Pregnancy is a period in which the intake of alcohol is not as socially accepted as in other periods of life, although the population and health professionals have not yet assumed a zero tolerance with alcohol during pregnancy. This is a period especially sensitive to teratogens since cell division is very high and since it is such an early stage of pregnancy the damage is very structural.

Precisely the FAS and FASD have a higher prevalence in comparison with other more known diseases, such as Down Syndrome or spine bifida, and are also 100% preventable, for this reason the health authorities report that there is no safe level of drinking during pregnancy. Although the society is informed, it is not aware of the dramatic damages related to alcohol consumption in this period of life. It is the first preventable cause of mental retardation and congenital defects.

Frequently these children affected by FASD receive a wrong diagnosis, such as hyperactivity, impulsivity, dyslexia or others, which leads to a wrong treatment that does not help to improve their development, performance and integration.

Although most pregnancies are intended, they are not planned. Unplanned pregnancies can put embryos at risk of being unintentionally exposed to alcohol in the earliest stage of pregnancy, when brain and facial development are particularly vulnerable to its effects. Alcohol is one of the last actions that is carried out when planning pregnancy, since it is the moment of diagnosis of pregnancy (at the end of early embryogenesis) the most common chosen moment to eliminate consumption.

In the scientific studies that estimate the prevalence of exposure to alcohol during pregnancy there is a great disparity of results, one of the main causes is the definition of pregnancy, time of interview and form of quantification.

The prevalence of pregnant women who admit alcohol intake during gestation has been reported from 12% to 45% (27)(13).

In Murcia 72.3% of women consumed alcohol in the periconceptional period: 52% up to the 7th week of gestation, 26.3% up to the 9th week of gestation and 23.2% up to the 11th week of gestation (28).

In Catalonia, the only data we have about alcohol during pregnancy is from a study performed in Barcelona in a low socioeconomic status population, by determining fatty acids ethyl esters in meconium, this study found that 45% of mothers consumed alcohol during pregnancy (30).

We know the prevalence of alcohol consumption in Spain from the Spanish National Survey on Alcohol and other Drugs (EDADES) (31). The latest survey shows a regular or occasional global alcohol consumption of almost three quarters of women of childbearing age and almost one in 10 women has had binge-drinking in the last 30 days (31).

In our study, the results show a maternal alcohol consumption prevalence of 54.8% at some point during pregnancy. The prevalence of alcohol consumption among pregnant women obtained have been lower than those obtained in the EDADES state surveys(31), and in the study carried out in Murcia using the Green Page (28), although, we have obtained higher prevalence of consumption than the study carried out in a low socioeconomic status population of Barcelona using meconium analysis(30).

We also wanted to make a space in the discussion to raise awareness about alcohol-free beers, which do contain alcohol, reaching up to 2 grams of alcohol per 200 milliliters of beer. This is a national problem since most of the population is unaware that alcohol-free beer contains alcohol, and as we have said before, there is no safe level of drinking during pregnancy.

## 9. LIMITATIONS AND STRENGTHS OF THE STUDY

The limitations of this study are the limitations of the studies carried out through a clinical interview. For this reason, the interviewers who carry out the green page are qualified and trained health professionals, with acquired skills that improve the screening capacity and the motivational framework in which it is carried out.

The results have not been accompanied by the screening of biomarkers due to economic limitations. However, the data on exposure to alcohol are similar or even somewhat higher than those reported through biomarker studies.

Memory bias exists, but the fact that this study has being performed 'face to face' in a clinical environment, of confidence and during the first trimester of pregnancy ensures that this impact can be minimized.

Special emphasis should be placed on memory bias, which plays an important role in this type of study. However, this bias is reduced as much as possible by conducting the interview in a clinical, supportive and confidential environment and during the early months of pregnancy, which ensures that the impact of this bias can be reduced.

The Green Page is a dynamic tool that requires continuous assessment based on the needs of the population. As Green Pages are made, needs are detected and included to improve data collection and subsequent monitoring.

And for the strengths of this study we highlight that it is a screening implemented in an entire community, in this case, in an entire region, regardless of ethnicity and socioeconomical status, which is representative of the Catalan / European population by its demographic characteristics.

## 10. CONCLUSION

Based on data obtained from an entire community, we conclude that the Green Page is a useful tool for quantifying prenatal alcohol exposure, and that its mere implantation has reduced prenatal alcohol exposure. We also concluded that it is a very useful and effective tool for diagnosing children at risk of developing some type of disorder related to prenatal alcohol exposure.

Including a carefully obtained GP questionnaire in pregnancy programs will help to detect, and prevent, the exposures to neurotoxic substances such as tobacco, alcohol and others illegal drugs. An increase in awareness and training of health care professional is needed, as well as alcohol risk perception by the parents. Total alcohol abstinence during pregnancy in both parents is highly recommendable.

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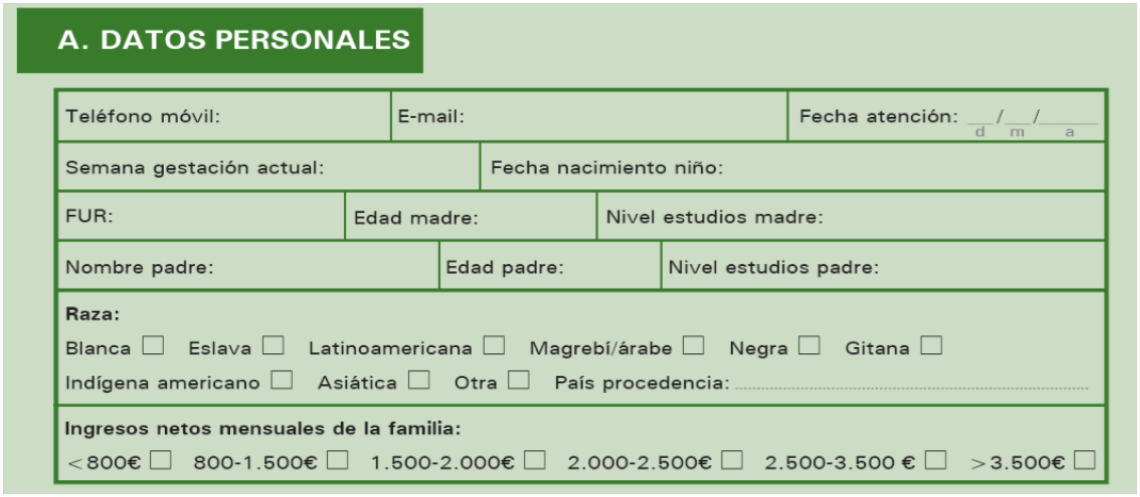
## 12. ANNEX

### 12.1. ANNEX 1: GREEN PAGE

This manual has been created to facilitate the handling and training with the green leaf of pregnancy and breastfeeding.

Reference: Ortega García JA, Sánchez Sauco MF, Jaimes Vega DC, Pernas Barahona A. Hoja verde. Creando ambientes más saludables durante el embarazo y lactancia materna. Unidad de Salud Medio ambiental Pediátrica. Murcia, España; 2013.

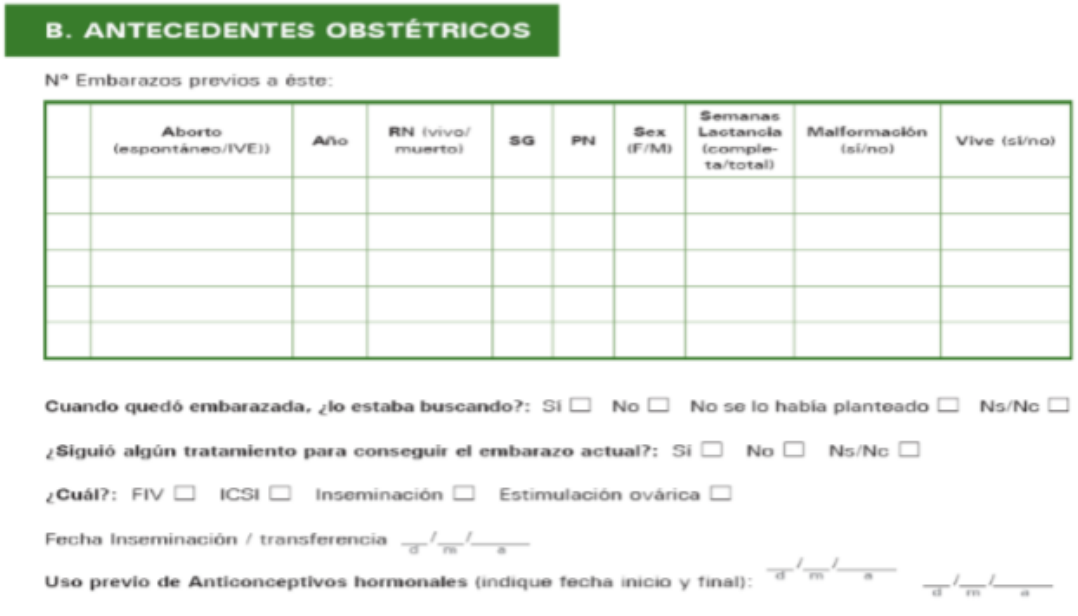


**A. DATOS PERSONALES**

| | | |
|---|---|---|
| Teléfono móvil: | E-mail: | Fecha atención: __/__/____ (d m a) |
| Semana gestación actual: | Fecha nacimiento niño: | |
| FUR: | Edad madre: | Nivel estudios madre: |
| Nombre padre: | Edad padre: | Nivel estudios padre: |

**Raza:**
Blanca ☐ Eslava ☐ Latinoamericana ☐ Magrebí/árabe ☐ Negra ☐ Gitana ☐
Indígena americano ☐ Asiática ☐ Otra ☐ País procedencia: .....

**Ingresos netos mensuales de la familia:**
<800€ ☐ 800-1.500€ ☐ 1.500-2.000€ ☐ 2.000-2.500€ ☐ 2.500-3.500 € ☐ >3.500€ ☐



**B. ANTECEDENTES OBSTÉTRICOS**

Nº Embarazos previos a éste:

| | Aborto (espontáneo/IVE)) | Año | RN (vivo/ muerto) | SG | PN | Sex (F/M) | Semanas Lactancia (comple-ta/total) | Malformación (si/no) | Vive (si/no) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

**Cuando quedó embarazada, ¿lo estaba buscando?:** Si ☐ No ☐ No se lo había planteado ☐ Ns/Nc ☐

**¿Siguió algún tratamiento para conseguir el embarazo actual?:** Si ☐ No ☐ Ns/Nc ☐

**¿Cuál?:** FIV ☐ ICSI ☐ Inseminación ☐ Estimulación ovárica ☐

Fecha Inseminación / transferencia __/__/____ (d m a)

**Uso previo de Anticonceptivos hormonales** (indique fecha inicio y final): __/__/____ (d m a) __/__/____ (d m a)

## C. RADIACIÓN IONIZANTE

**Pruebas médicas de radiaciones ionizantes en la etapa periconcepcional y embarazo:** Sí ☐ No ☐

**¿Cuál prueba?** (RX, TAC, dentista, otra): _____

**Fecha de realización de la prueba:** ___/___/_____ (d / m / a)

## D. FÁRMACOS / HOMEOPATÍA / HERBORISTERÍA / SUPLEMENTOS

**¿Ha tomado alguna medicación de forma esporádica o habitual?** (desde un mes antes del embarazo o lactancia).

| Fármaco o producto | Motivo | Posología | Fecha inicio | Fecha final o actual |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

## E. EXPOSICIONES EN EL TRABAJO Y AFICIONES

Indicar ocupación de los padres 3 meses antes de la FUR y especificar en caso de cambio.


**Riesgos ambientales asociados a las ocupaciones de los que viven en casa:** _____

_____

**¿Le preocupa alguna exposición a tóxicos medioambientales en el trabajo?:** Si ☐ No ☐ No lo sé ☐

**En caso afirmativo explicar:** _____

**¿Se llevan la ropa o zapatos del trabajo a la casa?:** Si ☐ No ☐ No lo sé ☐

**Tienen alguna afición que le exponga a algunas sustancias químicas:**

Aeromodelismo ☐ Fotografía/revelado ☐ Maquetación ☐ Restauración muebles ☐

Motociclismo ☐ Mecánica ☐ Pintura ☐ Ninguna ☐ Otros: _____

## F. TABACO Y OTRAS DROGAS

| TABACO | | Madre | Padre | Otro en domicilio |
|---|---|---|---|---|
| **Fumaba algo antes del embarazo** (periconcepcional) | Sí/No/Nunca | | | |
| **¿Cuánto fumaba?** | cigarrillos/día | | | |
| **Edad inicio** | años | | | |
| **¿Cambió el consumo debido al embarazo?** | Sí/No | | | |
| **¿Cuándo cambio?** | SG | | | |
| **¿Cuánto fuma ahora?** | cigarrillos/día | | | |
| **¿Le gustaría dejar de fumar?** | Sí/No | | | |
| **¿Ha pensando en hacerlo próximamente?** | Sí/No | | | |
| **Exposición a humo de tabaco de formas pasiva** (amigos o familiares) | Nada<br>Poco<br>Bastante<br>Mucho | | | |
| **¿Ha podido estar expuesta a otras drogas en algún momento del embarazo o desde 3 meses antes del embarazo?** | Cannabis ☐<br>Cocaína ☐<br>Heroína ☐<br>Otras ☐<br>Ninguno ☐ | En caso afirmativo explique: | | |

## G. EXPOSICIÓN AL ALCOHOL

Por favor, indique el número de vasos o copas que bebía en cada etapa (señale debajo de donde corresponda...1-3 por mes, 1 por semana, 1 día, etc.).

| Madre periconcepcional 3 meses antes del embarazo | Nunca o <1 mes | 1-3 x mes | 1 x sem | 2-4 x sem | 5-6 x sem | 1 x día | 2-3 x día | 4-5 x día | +6 x día | gramos OH/día |
|---|---|---|---|---|---|---|---|---|---|---|
| a Vino tinto, blanco, rosado y vermú (1 vaso, 125 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | a |
| | 0 | 0.6 | 1.42 | 4.28 | 7.85 | 10 | 25 | 45 | 60 | |
| b Cerveza (1 caña o botellín 1/5, 200 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | b |
| | 0 | 0.6 | 1.42 | 4.28 | 7.85 | 10 | 25 | 45 | 60 | |
| c Licores (20-25º): de frutas (manzana), de crema (Catalana, Bayleys) (1 copa, 50 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | c |
| | 0 | 0.75 | 2.1 | 6.43 | 11.78 | 15 | 37.5 | 67.5 | 90 | |
| d Brandy, ginebra, ron, whisky, vodka, aguardientes 40º (1 copa, 50 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | d |
| | 0 | 1.2 | 2.84 | 8.56 | 15.7 | 20 | 50 | 90 | 120 | |
| e Cerveza sin alcohol (200 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | e |
| | 0 | 0.13 | 0.28 | 0.85 | 1.57 | 2 | 5 | 9 | 12 | |
| | | | | | | | | | a+b+c+d+e gramos total de alcohol/día | |

**Número de atracones (>/= 5 UBE = 50 gr) desde FUR a la fecha actual:** .....

**¿Cambió el consumo debido al embarazo?** Sí ☐ → Lo eliminó ☐ / Disminuyó ☐ No ☐

**¿Cuándo cambió?** Antes de FUR ☐ Indique semanas de gestación ☐

Durante el embarazo ☐ Semanas de gestación ☐ Durante la lactancia ☐

| Madre actualmente | Nunca o < 1 mes | 1-3 x mes | 1 x sem | 2-4 x sem | 5-6 x sem | 1 x día | 2-3 x día | 4-5 x día | +6 x día | gramos OH/día |
|---|---|---|---|---|---|---|---|---|---|---|
| a Vino tinto, blanco, rosado y vermú (1 vaso, 125 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | a |
| | 0 | 0.6 | 1.42 | 4.28 | 7.85 | 10 | 25 | 45 | 60 | |
| b Cerveza (1 caña o botellín 1/5, 200 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | b |
| | 0 | 0.6 | 1.42 | 4.28 | 7.85 | 10 | 25 | 45 | 60 | |
| c Licores (20-25°): de frutas (manzana), de crema (Catalana, Bayleys) (1 copa, 50 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | c |
| | 0 | 0.75 | 2.1 | 6.43 | 11.78 | 15 | 37.5 | 67.5 | 90 | |
| d Brandy, ginebra, ron, whisky, vodka, aguardientes 40° (1 copa, 50 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | d |
| | 0 | 1.2 | 2.84 | 8.56 | 15.7 | 20 | 50 | 90 | 120 | |
| e Cerveza sin alcohol (200 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | e |
| | 0 | 0.13 | 0.28 | 0.85 | 1.57 | 2 | 5 | 9 | 12 | |
| a + b + c + d + e gramos total de alcohol/día | | | | | | | | | | |

| El padre durante la espermatogénesis | Nunca o < 1 mes | 1-3 x mes | 1 x sem | 2-4 x sem | 5-6 x sem | 1 x día | 2-3 x día | 4-5 x día | +6 x día | gramos OH/día |
|---|---|---|---|---|---|---|---|---|---|---|
| a Vino tinto, blanco, rosado y vermú (1 vaso, 125 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | a |
| | 0 | 0.6 | 1.42 | 4.28 | 7.85 | 10 | 25 | 45 | 60 | |
| b Cerveza (1 caña o botellín 1/5, 200 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | b |
| | 0 | 0.6 | 1.42 | 4.28 | 7.85 | 10 | 25 | 45 | 60 | |
| c Licores (20-25°): de frutas (manzana), de crema (Catalana, Bayleys) (1 copa, 50 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | c |
| | 0 | 0.75 | 2.1 | 6.43 | 11.78 | 15 | 37.5 | 67.5 | 90 | |
| d Brandy, ginebra, ron, whisky, vodka, aguardientes 40° (1 copa, 50 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | d |
| | 0 | 1.2 | 2.84 | 8.56 | 15.7 | 20 | 50 | 90 | 120 | |
| e Cerveza sin alcohol (200 cc) | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ | e |
| | 0 | 0.13 | 0.28 | 0.85 | 1.57 | 2 | 5 | 9 | 12 | |
| a + b + c + d + e gramos total de alcohol/día | | | | | | | | | | |

**El padre actualmente ha cambiado su consumo:** Sí ☐ → Ha aumentado ☐ / Ha disminuido ☐ No ☐

## H. EXPOSICIONES EN EL HOGAR, JARDÍN Y HUERTO

**Años construcción de la vivienda:**_____ **¿Tipo de vivienda?:** Piso (altura) ☐ Dúplex ☐ Casa de pueblo ☐

**¿Ha tenido problemas en casa de hormigas, cucarachas, roedores, etc...?:** Sí ☐ No ☐

**Utiliza spray, polvos, enchufes u otros plaguicidas en casa o huerto:** Sí ☐ No ☐

**Cuáles:**_____ **¿Cuánto le dura un envase de pesticida 1.000 cc?** _____

## I. PERCEPCIÓN DE RIESGOS

**¿Están preocupados por algunos riesgos ambientales en su casa o barrio?** Madre:_____ Padre:_____

Observaciones:_____

## 12.2. ANNEX 2: CONSENT INFORMED

### Hoja de Consentimiento Informado

**(Copia futuros Padres)**

Yo, .....(nombre y apellidos),
en calidad de... ..... (relación con el que vienen a consulta)
Yo, ..... (nombre y apellidos),
en calidad de... ..... (parentesco)

- Hemos leído la hoja de información que se nos ha entregado.
- Hemos podido hacer preguntas sobre el estudio.
- Hemos recibido suficiente información sobre el estudio.
- Hemos hablado con....., quien nos ha aclarado las dudas.
- Comprendemos que nuestra participación es voluntaria.
- Comprendemos que podemos retirarnos del estudio:
  - -Cuando queramos
  - -Sin tener que dar explicaciones
  - -Sin que esto repercuta en los cuidados médicos
- Comprendemos que el estudio está diseñado para incrementar los conocimientos médicos.
- Comprendemos que todos los resultados son confidenciales y que sólo nosotros, si los pedimos, y los responsables del estudio los conoceremos.

- Prestamos libremente nuestra conformidad para participar en el estudio.

| | |
|---|---|
| Firma del padre o tutor | Firma de la madre o tutor |
| DNI: ..... | DNI: ..... |

Fecha y lugar: ....., a ..... de ..... de 20....

**Indique si desea seguir manteniendo información del proyecto: Sí No**
**Ns/Nc Teléfono de contacto de la familia:**
**Dirección postal de la familia:**
**Email:**

## Hoja de Consentimiento Informado

Yo, ..... (nombre y apellidos), en calidad de... ..... (relación de parentesco)
Yo, ..... (nombre y apellidos), en calidad de... ..... (relación de parentesco)

- Hemos leído la hoja de información que se nos ha entregado.
- Hemos podido hacer preguntas sobre el estudio.
- Hemos recibido suficiente información sobre el estudio.
- Hemos hablado con....., quien nos ha aclarado las dudas.
- Comprendemos que nuestra participación es voluntaria.
- Comprendemos que podemos retirarnos del estudio:
  - -Cuando queramos
  - -Sin tener que dar explicaciones
  - -Sin que esto repercuta en los cuidados médicos
- Comprendemos que el estudio está diseñado para incrementar los conocimientos médicos.
- Comprendemos que todos los resultados son confidenciales y que sólo nosotros, si los pedimos, y los responsables del estudio los conoceremos.

- Prestamos libremente nuestra conformidad para participar en el estudio.

| | |
|---|---|
| Firma del padre o tutor | Firma de la madre o tutor |
| DNI: ..... | DNI: ..... |

Fecha y lugar: ....., a ..... de ..... de 20....

**Indique si desea seguir manteniendo información del proyecto: Sí No**
**Ns/Nc Teléfono de contacto de la familia:**
**Dirección postal de la familia:**
**Email:**