FETAL ALCOHOL SPECTRUM DISORDERS IN PEDIATRICS
FASD AND THE PEDIATRICIAN

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Fetal alcohol syndrome (FAS) is a complex and malformative condition due to the teratogenic effect of alcohol consumed during pregnancy. Several epidemiological studies have shown that maternal alcohol use during pregnancy is the most common preventable cause of mental retardation in childhood. The effects of alcohol on the fetus range from abortion to a spectrum of clinical manifestations called Fetal Alcohol Spectrum Disorders (FASD) that includes partial FAS (PFAS), neonatal Alcohol Related Birth Defects (ARBD) and Alcohol Related Neurodevelopmental Disorders (ARND) up to the most severe disease which is the so-called FAS. Biomed Rev 2018; 29: 27-35

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Key messages (Highlights)
1) FASD represents the most common acquired mental retardation, which is totally preventable.
2) The threshold dose of teratogenic alcohol damage is not known, therefore absolute abstention during pregnancy is indicated.
3) The diagnosis of FASD is “by exclusion” and is based essentially on clinical suspicion and confirmation of alcohol intake during pregnancy, therefore all genetic conditions with similar clinical characteristics must be sought.

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INTRODUCTION

Fetus alcohol syndrome (FAS) is a complex malformative condition of the newborn and the child, described by Lemoine (1) and classified by K. Jones (2, 3), due to the teratogenic effect of alcohol taken during pregnancy (4–16). It is the most common cause of mental retardation acquired in childhood, therefore totally avoidable, through the complete abstention of the pregnant woman from the consumption of alcohol. The effects of alcohol on the fetus range from the absence of damage to abortion, including a spectrum of clinical manifestations called FASD (Fetal Alcohol Spectrum Disorders) which, in addition to FAS, includes partial FAS (PFAS), associated neonatal congenital defects (Alcohol Related Birth Defects, ARBD) and neurological development disorders (Alcohol Related Neurodevelopmental Disorders, ARND) (17). Although FASD is a common cause of disability, there are still no definite data on its incidence and prevalence in Italy or in the world, but only sporadic reports. This probably leads to an underestimation of the problem and does not facilitate the correct diagnosis and the possible rehabilitation of numerous children with mental retardation. However, the global prevalence of FASD is about 0.77%, the European prevalence is 0.19%, while in the US it is about 2-5%. The only Italian data concerns the prevalence in Lazio, which for the FAS is 3.7-7.4:1000 and for the FASD is 2-4% (18–22).

WHY CAN THE PEDIATRICIAN SUSPECT IT?

In the neonatal age, FAS can be suspected in the presence of a small gestational age with microcephaly and typical dysmorphisms (23–25). The microcephaly data is salient because the preterm newborns are generally relatively macrocephalic. During childhood, the diagnosis is easier because, in addition to the growth defect and facial dysmorphic signs, psychomotor retardation, behavioral disorders and attention and concentration deficits can be detected. In adolescence, to the typical signs of the pediatric age can be added behavioral, scholastic and, above all, social problems.

The pediatrician should refine the diagnostic sensitivity to understand the behavior of the mothers, which demonstrate responsibility, control, balance, care and attention to the newborn. Indeed, it has been shown that mothers who have substantial defects in these spheres, are those who drink even during breastfeeding, exposing the infant to an increased risk of impaired abilities at 6 years (26), even if they did not drink during pregnancy. In fact, the alcohol for 30-60 min after ingestion, maintains in the milk the same levels of maternal blood, in quantities equal to 5-6% of the ingested dose and with a half capacity to be metabolized by the newborn.

CLINICAL CRITERIA FOR DIAGNOSIS

Due to the lack of diagnostic genetic or biochemical tests, the decisive step in identifying a child with FASD is to ascertain maternal alcohol consumption during pregnancy (27–32). The absence of this data, very often difficult to obtain due to the guilty feelings of mothers, however, does not exclude the diagnosis, which must be formalized following the recent guidelines (33, 34) that are based on the multidisciplinary approach to the mother-child dyad and aimed at analyzing 3 essential aspects of the syndrome (26, 35–37):

1) Morphological abnormalities of the newborn,
2) Neuropsychological, intellectual and social development of the child,
3) Maternal risk factors.

The diagnostic guidelines subdivide the FASD in various forms.

I. FAS (all A-D criteria required)

With or without confirmation of maternal intake of alcohol during pregnancy

A. Presence of two or more facial abnormalities between:
   1. Short palpebral fissures (< 10th percentile)
   2. Thin upper lip (score 4 or 5)
   3. Long and thin philtrum (score 4 or 5)

B. Pre-postnatal growth rate (height and/or weight < 10th percentile per age)

C. Microcephaly or cerebral structural anomalies or recurrent non-febrile convulsions

D. Neurobehavioral deficits (< or > of 3 years)
   < 3 years: mental retardation: > 1.5 SD below average
   > 3 years
      1) With cognitive defect
         a) Global: general conceptual ability or verbal, spatial, performance IQ: > 1.5 SD below average
         b) At least 1 neuro-behavioral domain among, executive functions, language, memory, visual-spatial ability: > 1.5 SD below average
      2) With behavioral disorders, without cognitive defect.
         Deficit in at least 1 domain between mood regulation, attention, control of the pulses:
         > 1.5 SD below the average
II - partial FAS
Confirmation of maternal alcohol intake during pregnancy:
A-B criteria required
Without confirmation, required A-C criteria
A. Presence of two or more of the facial anomalies (point A of the complete FAS)
B. Neurobehavioral deficit (point D of the complete FAS)
C. Pre- and/or postnatal growth retardation

III - ARND required criteria A and B (diagnosis cannot be placed in children <3 years)
A. Confirmation of maternal intake of alcohol during pregnancy
B. Cognitive-behavioral abnormalities (point D of the complete FAS)

IV - ARBD required criteria A and B
A. Confirmation of maternal intake of alcohol during pregnancy
B. Congenital structural defects (one or more of the heart, kidneys, skeletal, ears, eyes and minor anomalies)

CLINICAL PICTURE AND MEDICAL COMPLICATIONS

Growth retardation: individuals with FASD, almost constantly, show postnatal growth retardation that occurs during the prenatal period because exposure to fetal alcohol, especially in the third trimester, strongly reduces somatic development. Infants may be small for gestational age and remain below the stature average even during the development. Some children with FASD, probably because they were not exposed to alcohol in the last trimester, may have normal growth parameters but, secondarily, develop learning and cognitive deficits.

Facial anomalies
Subjects with FAS have 3 major specific abnormalities such as: short palpebral fissures (equal to or lower than the 10th percentile), elongated and flattened nasolabial philtrum and thin upper lip. They may also have minor associated dimorphisms, such as: epicanthus, hypertelorism, flat nasal root with a short nose with antiverse nostrils, hypoplasia of the cheekbones, anomalies of positioning of the ears with a “railway track” appearance of the antihelix cartilage and micrognathia. (Fig. 1)

The identification of the three main facial changes, typical of FASD, can be performed using some standard reference guides, such as the lips and philtrum, (Fig. 2) that transform some clinical aspects into numerical data (score 1-5) and with the aid of the percentiles of growth percentages, by age and sex, of the palpebral fissures, interpupillary and intercanthal distances and of the filter, for the detection of which is necessary to have a rigid ruler, possibly transparent.

Structural Congenital Defects
These include anomalies of various organs such as:
- Heart: (25-50%): inter-atrial or inter-ventricular defects, cono-truncal anomalies or large vessels.
- Kidneys (4%): aplasia, hypoplasia, renal dysplasias, horseshoe kidneys, rhen-ureteral duplications.
- Skeleton: with radio-ulnar synostosis, vertebral segmentation defects with cervical vertebrae fusion (50%), ankylosis of large joints, scoliosis (15%).
- Ears: mixed (90%) or sensorineural (30%) hearing loss.
- Eyes: microphthalmia, strabismus, palpebral ptosis and retinal vascular anomalies with associated visual defect.
- Teeth: frequent caries, ogival palate and Class III malocclusion with growth.

Figure 1. Standard guide for the lip and the philtrum (SCORE 1-2 Normal; 3-5 Possible FAS).
Minor dysmorphic anomalies such as: hypoplastic nails, brevity and clinodactyly of the fifth finger, camptodactyly, handheld “hockey stick” and pectus excavatum/carinatum.

**Abnormalities of the Central Nervous System**

Numerous studies on the damage due to intrauterine exposure to alcohol show a range of short-term and long-term cognitive and behavioral outcomes deriving from structural and functional central nervous system abnormalities.

The main structural alteration of FASD is microcephaly, often accompanied by low overall growth. Magnetic resonance imaging (MRI) studies show an overall reduction in brain volume and a disorganization of the central nervous system (CNS) (38–50), with specific structural anomalies of alcohol vulnerable areas such as corpus callosum (agenesis, hypoplasia), cerebral cortex, cerebellum, caudate nucleus and hippocampus have been correlated with specific functional alterations (51–54).

Functional disorders include neurological signs such as spasticity, asymmetries in reflexes and, above all, seizures, whose incidence is not yet clear but which involve confirmation with electroencephalogram (EEG) and possibly therapy (55–59).

**CONFIRMATION EXAMS**

The definition of dysmorphic signs requires that precise measurements of stature, weight and cranial circumference are made, as well as the assessment of the length of the eyelid slits and of the philtrum. All these data are pathological if they are below the 10th percentile. Also, the appearance of the filter and of the upper lip, which are qualitative data, have been made measurable as quantitative data by the use of the Lip-Philtrum Guide. Once a syndromic picture is suspected, it is advisable to obtain confirmation of maternal intake of alcohol during pregnancy (maternal risk factors, adoption from Eastern European countries) and to search for congenital anomalies associated with brain, heart and abdominal ultrasounds, X-rays of the skeleton and brain MRI, EEG, audiometric test and eye examination, as well as to perform the genetic screening tests such as the examination of the karyotype and the CGH-array (60, 61). In this way, it is possible to make the differential diagnosis with the syndromes that have signs in common, such as chromosomal diseases and micro-deletions/duplications or other genetic syndromes (Table 1).

![Figure 2. Typical facial signs of FAS children with essential characteristics such as: the short palpebral fissures, the elongated and flattened nasolabial philtrum and the thin upper lip. The dysmorphologic parameters must be detected at all ages, but if the patient’s facial signs have eased over time, the diagnosis of facial anomalies should be based on the period in which they were most expressed, possibly with the help of photos. In fact, it is important to observe how the facies of FAS sufferers remain basically unchanged over time.](image-url)
Table 1. Differential FASD diagnosis versus other syndromes

| Syndromes                        | Common signs with FASD                                      | Differential features                                                                 |
|----------------------------------|-------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Aarskog Syndrome                 | Small saddle nose, anteverse nostrils, ample philtrum, hypertelorism | Round face, palpebral ptosis, fold under the lower lip, dental rash problems            |
| Williams Syndrome                | Short palpebral fissures, anteverse nostrils, elongated philtrum, epicanthus, saddle nose | Wide mouth, star pattern of iris, peri orbital swelling, cartilage disorders            |
| Noonan Syndrome                  | Lowered nasal bridge, hypertelorism, epicanthus             | Keratoconus, palpebral ptosis, broad mouth with protrusion of the upper lip             |
| Dubowitz Syndrome                | Short palpebral fissures, hypertelorism, epicanthus         | Low supraorbital ridge with nose bridge at the level of the forehead                    |
| Brachmann-De Lange Syndrome      | Elongated philtrum, thinned upper lip, depressed nasal bridge | Single bush eyebrow along the forehead, long eyelashes, short limbs, acute arch palate  |
| Toluene embryopathy              | Short palpebral fissures, median face hypoplasia, thinned upper lip | Micronathia, open front fontanelle, hair anomalies, bifrontal narrowing                 |
| Fetal Hydantoin Syndrome, also called Fetal Dilantin Syndrome | Hypertelorism, depressed nasal bridge                       | Short nose with upper arched lip                                                      |
| Fetal Valproate Syndrome         | Anteverse niches, elongated philtrum, hypertelorism         | High forehead, infraorbital fold, small mouth                                           |
| Effects on the fetus of maternal phenylketonuria | Epicanthus, short palpebral rhymes, flattened philtrum, thin upper lip | Small saddle nose, prominent glabella, rounded face                                     |

In fact, a diagnosis of FASD in a child with disability cannot be automatically set-up simply because the mother has taken alcohol during pregnancy and, especially if this confirmation is missing, the diagnosis of FASD must be considered as a diagnosis of exclusion (27, 28, 62).

**INTELLECTUAL PROGNOSIS AND SURVIVAL**

In patients with FASD, when mental retardation is present, it persists, but with improvements related to rehabilitation therapies. Psycho-behavioral problems, if not recognized and early treated, can promote the deterioration of quality of life. Long-lasting mental retardation could overlap with alcohol use disorders during the adult life (63–66).

It was found (67–69) that among people aged 6 to 51 years affected by FASD:
- 94% have mental health problems and in 23% of these people mental illness requires hospital assistance
- 83% of adults have problems with addiction
- 79% of adults have employment problems
- Instead, in boys over the age of 12 it has been reported that: 61% have a disruptive school experience
- 60% have problems with the law
- 49% assume inappropriate sexual behavior
- 35% have alcohol/drug problems

**KNOWN MEDICAL COMPLICATIONS**

Although recently the use of alcohol in pregnancy has been correlated with an increased risk of sudden infant death syndrome (70), the main complications attributable to FASD frameworks are mainly related to neurocognitive and behavioral problems. Among the cognitive deficits, the most common are the linguistic difficulties, both of production and of understanding, and the disturbances of the attention (71).

However, mental retardation is not a constant feature of the
syndrome because the child’s IQ can vary from a normal range to a severe disability. Deficits in executive functions (gradual reasoning, planning, judgment, problem solving, monitoring) and behavioral disorders (difficulty in taking appropriate behavior, emotional lability, poor academic performance and lack of social interaction) are very frequent and enormously impair social adaptation (72).

CONCLUSION

The issue of lifelong disabilities caused by alcohol drinking during pregnancy is quite problematic at familial, individual and societal level. As far as a nontoxic consumption behavior during gestation cannot be established, for the extremely individual conditions of vulnerability to alcohol (73), the only suggestion for women planning pregnancies, or during gestation and lactation is to totally avoid the consumption of alcoholic beverages.

CONFLICT OF INTEREST STATEMENT

The authors certify that they have no affiliations with or involvement in any organization with any financial interest in the subject matter discussed in this review article.

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