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Italian Guidelines for the diagnosis and treatment of Fetal Alcohol Spectrum Disorders: diagnostic criteria

GINEVRA MICANGELI[1], MICHELA MENGHI[1], ROBERTO PAPARELLA[1], MAURO CECCANTI[2], GIOVANNA CORIALE[3], DANIELA FIORENTINO[4], GIAMPIERO FERRAGUTI[5], MARCO FIORE[6], LUIGI TARANI[1]; INTERDISCIPLINARY STUDY GROUPS* SAPIENZA, ISS, ISTAT, AIDEFAD, SITAC, SIFASD, FIMMG-LAZIO, SIPPS, SIMPESV, CIPE

[1]Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome, Italy; [2]SITAC, Società Italiana per il Trattamento dell'Alcolismo e le sue Complicanze, Rome, Italy; [3]CRARL Lazio, ASL Roma 1, Rome, Italy; [4]ASL Rieti, Rieti, Italy; [5]Department of Experimental Medicine, Sapienza University of Rome, Italy; [6]Institute of Biochemistry and Cell Biology (IBBC-CNR), c/o Department of Sensory Organs, Sapienza University of Rome, Italy.

Summary. Fetal Alcohol Spectrum Disorders (FASD) encompass a spectrum of clinical manifestations resulting from maternal alcohol consumption during pregnancy. This condition presents with diverse anomalies including intrauterine and extrauterine growth retardation, phenotypic abnormalities, cerebral structural anomalies, cognitive delays, and behavioral abnormalities. Regrettably, FASD remains an irreversible and epigenetic condition, with total abstention from alcohol during pregnancy being the sole effective preventive measure due to the absence of a viable therapy. Diagnosis typically occurs postnatally, based on a combination of alcohol exposure history and the presence of aforementioned physical or behavioral abnormalities. The diagnosis is not always easy to make even in the post-natal period due to the different subtypes of existing FASD. Indeed, only some of these subtypes cause behavioral or neurodevelopmental abnormalities in the absence of pathognomic physical anomalies. Although the diagnostic criteria are useful, unfortunately, there is a heterogeneity resulting from the different guidelines that are used in different countries. The aim of our review, based on a literature search of online databases including Medline, Medline Complete, PubMed, and Google Scholar, is therefore to provide an overview of the diagnostic criteria used in Italy.

Key words. Alcohol-related birth defects, fetal alcohol spectrum disorders, fetal alcohol syndrome, pediatrician, prenatal alcohol exposure.

Linee guida italiane per la diagnosi e il trattamento dei disturbi dello spettro feto-alcolico: criteri diagnostici.

Riassunto. I disturbi dello spettro feto-alcolico (FASD) comprendono una serie di manifestazioni cliniche derivanti dal consumo di alcol da parte della madre durante la gravidanza. Questa condizione si presenta con diverse anomalie, tra cui ritardo della crescita intrauterina ed extrauterina, anomalie fenotipiche, anomalie strutturali cerebrali, ritardi cognitivi e anomalie comportamentali. Purtroppo, la FASD rimane una condizione irreversibile ed epigenetica, con l'astensione totale dall'alcol durante la gravidanza come unica misura preventiva efficace a causa dell'assenza di una terapia praticabile. La diagnosi avviene in genere nel periodo postnatale, in base a una combinazione di anamnesi di esposizione all'alcol e alla presenza delle suddette anomalie fisiche o comportamentali. La diagnosi non è sempre facile da fare anche nel periodo postnatale a causa dei diversi sottotipi di FASD esistenti. Infatti, solo alcuni di questi sottotipi causano anomalie comportamentali o neuroevolutive in assenza di anomalie fisiche patognomoniche. Sebbene i criteri diagnostici siano utili, sfortunatamente, esiste un'eterogeneità derivante dalle diverse linee guida utilizzate nei diversi Paesi. Lo scopo della nostra revisione, basata su una ricerca bibliografica di banche dati online tra cui Medline, Medline Complete, PubMed e Google Scholar, è quindi quello di fornire una panoramica dei criteri diagnostici utilizzati in Italia.

Parole chiave. Difetti congeniti correlati all'alcol, disturbi dello spettro feto-alcolico, esposizione prenatale all'alcol, pediatra, sindrome feto-alcolica.

Introduction

Fetal Alcohol Spectrum Disorders (FASD) is an umbrella term[1-6] that encompasses a range of conditions caused by prenatal alcohol exposure (PAE) such as:

- *Fetal Alcohol Syndrome* (FAS): this is the most severe form of FASD and is characterized by a specific set of physical, cognitive, and behavioral features[7,8];
- *Partial Fetal Alcohol Syndrome* (pFAS): some diagnostic systems or clinicians may use the term "partial FAS" to describe individuals who exhibit some, but not all, of the characteristic features of Fetal Alcohol Syndrome[9];
- *Alcohol-Related Neurodevelopmental Disorder* (ARND): this category is used when there are central nervous system abnormalities (CNS) and cognitive or behavioral impairments but without the physical features associated with FAS[10];
- *Alcohol-Related Birth Defects* (ARBD): this catego-

ry may be used when physical abnormalities are present without the characteristic facial features of FAS[11].

Notably, the terminology and diagnostic criteria may vary across regions and medical professionals[12-15]. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes criteria for Neurodevelopmental Disorders associated with PAE, but it doesn't use the specific term pFAS[16-19]. Clinicians may use a combination of features and assessments to diagnose individuals within the broader FASD spectrum[20]. In particular, FAS is considered one of the most severe outcomes of PAE[21]. The developing fetus is particularly vulnerable to the effects of alcohol because alcohol crosses the placenta and can interfere with the normal development of the baby's organs and tissues[22].

The key features of FAS include:

- *facial abnormalities*: children with FAS may have distinctive facial features, such as a thin upper lip, a smooth philtrum (the groove between the nose and upper lip), and small eye openings;
- *growth deficiencies*: FAS can lead to growth problems, both before and after birth. Babies born with FAS may have lower birth weight and length[23];
- *CNS abnormalities*: alcohol exposure can affect the development and function of the central nervous system, leading to cognitive and behavioral issues[24-29]. Children with FAS may have learning disabilities, developmental delays, poor impulse control, and attention problems[7,30];
- *organ dysfunction*: alcohol exposure can also affect the development and function of various organs, potentially leading to heart defects, kidney problems, and other abnormalities.

Furthermore, the severity of FAS can vary, and not all individuals with prenatal alcohol exposure will exhibit the same set of features[10,15,31,32].

Epidemiology

The epidemiology of FASD involves studying the incidence, prevalence, risk factors, and distribution of these disorders in populations[33]. Accurate epidemiological data can be challenging to obtain because FASD encompasses a spectrum of conditions, and not all affected individuals may be diagnosed[30]. Additionally, underreporting and misdiagnoses can contribute to the complexity of obtaining precise epidemiological figures[34,35].

The prevalence of FASD varies across different populations and regions; estimates suggest that FASD is a global health concern, with prevalence rates ranging from 1% to 5% in certain high-risk populations[35,36]. However, these figures may not capture the full extent of the problem due to underdiagnoses and varying diagnostic criteria[37].

PAE is the primary risk factor for FASD, along with others such as timing, frequency, and quantity of alcohol consumption during pregnancy[36,38]. Maternal age, socioeconomic status, and access to healthcare may also play a role[31]. FASD is often underreported and misdiagnosed due to a lack of awareness, limited access to specialized diagnostic services, and the variability of symptoms; many individuals with FASD may not receive a diagnosis until later in life, if at all[11,39].

Efforts to improve the understanding and surveillance of FASD include increased awareness among healthcare professionals, enhanced prenatal education and improved access to diagnostic services. Early identification and intervention are crucial for providing support and improving outcomes for individuals with FASD. Ongoing research and public health initiatives aim to address the challenges associated with the epidemiology of FASD and enhance prevention and intervention strategies. According to a 2011 study based on 607 children born in 7 hospitals in different Italian regions, the prevalence of PAE was found to be 7.9%. As highlighted in the ISS press release dated September 1st, 2021, in 2011 the prevalence estimates of FAS and FASD were 1.2 and 63 per 1000 live births, respectively[35,40,41].

According to the WHO Global Status Report on Alcohol and Health 2018, countries in the European Region exhibit the highest prevalence of alcohol consumption during pregnancy (of any quantity), averaging at 25%. Even more alarming is the data indicating that in 2.7% of cases alcohol consumption occurs in a "binge drinking" manner, i.e. "drinking to get drunk", the most harmful form of intake, especially with regards to FASD[42,43]. The prevalence estimates of alcohol consumption among pregnant women mirror the alcohol intake of the general population in the country under investigation, similarly to the varied prevalence estimates of FAS and FASD across different populations and studies within the same community[35,44]. According to recent WHO estimates, 65.5% of women of childbearing age in the European Region consume alcohol, and given that almost half of pregnancies are unplanned (42%), the risk of alcohol consumption during the early stages of gestation is very high[45].

Given the clinical heterogeneity, our review aims to identify the comprehensive diagnostic criteria for FASD used in Italy. The literature for this review was sourced from online databases including Medline, Medline Complete, PubMed, and Google Scholar, utilizing search terms such as fetal alcohol spectrum disorders, fetal alcohol syndrome, prenatal alcohol exposure, and alcohol-related birth defects. The objective of our work was also to provide healthcare professionals with an overview of the different existing guidelines with particular attention to those currently used in Italy.

Etiology

The primary and well-established cause of FASD is PAE. Alcohol crosses the placenta and can impact

the developing fetus at various stages of pregnancy[8,46]. The risk is present at any time during pregnancy, and the severity of the effects may depend on factors such as the timing, amount, and pattern of alcohol consumption[47]. The effects of PAE can vary depending on the timing of the pregnancy. Critical periods of vulnerability exist when specific organs and systems undergo crucial development[8,48-51]. For instance, the CNS is particularly sensitive to alcohol exposure throughout pregnancy[21,52-56].

A dose-response relationship exists between the amount of alcohol consumed during pregnancy and the risk and severity of FASD. Higher levels of alcohol consumption are typically linked with an increased risk of adverse outcomes[47,57]. However, not all individuals exposed to alcohol during pregnancy develop FASD, indicating significant individual variability in susceptibility. Factors such as genetic predisposition, maternal health, nutritional status, and other environmental influences may contribute to this variability[13,57].

The mechanisms through which alcohol inflicts damage on the developing fetus are complex and multifaceted. Alcohol can interfere with cell proliferation, migration, and differentiation, thereby resulting in structural abnormalities in organs and tissues[58,59]. Additionally, it can disrupt neurotransmitter systems in the developing brain, affecting cognitive and behavioral functions[60]. FASD should be considered a preventable condition, with abstention from alcohol during pregnancy being the most effective preventive measure[61]. Early and accurate diagnosis of FASD is paramount for offering appropriate interventions and support for affected individuals and their families[62-64].

Diagnostic criteria

The diagnostic criteria for FAS typically encompass a combination of physical, developmental, and behavioral features[23,37]. These criteria may exhibit slight variations depending on the diagnostic system or guidelines employed by healthcare professionals[33,37,39,62,65-73].

Over the years, different guidelines for diagnosis have been developed by different research groups including:

- the Institute of Medicine Guidelines (IOM)[74];
- the 4-Digit Diagnostic Code[75];
- the Hoyme Updated Clinical Guidelines[37];
- the Canadian FASD Guidelines[76];
- the Centers for Disease Control and Prevention (CDC) Guidelines[77];
- the British Medical Association Guidelines (BMA Board of Science)[78];
- the Australian Guide to the diagnosis of FASD[79].

The absence of universally accepted diagnostic criteria on an international scale renders the diagnosis of FAS/FASD a complex, continuously evolving, and ongoing challenge[8,31,37]. In Italy, the diagnosis is based on the Hoyme criteria, with the latest updated criteria from 2016 presented in tables 1-4[37].

Table 1. The table shows the diagnostic criteria proposed by Hoyme for FAS[37,39].

I. FAS – Fetal Alcohol Syndrome

(**With or without documented** prenatal alcohol exposure)
Diagnosis of FAS requires all features, A-D:

A. A characteristic pattern of minor facial anomalies including ≥ of the following
1. Short palpebral fissures (≤10th centile)
2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)

B. Prenatal and/or postnatal growth deficiency
1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if available)

C. Deficient brain growth abnormal morphogenesis or abnormal neurophysiology including ≥ of the following
1. Head circumference ≤10th percentile
2. Structural brain anomalies
3. Recurrent non-febrile seizures (other causes of seizures having been ruled out)

D. Neurobehavioral impairments
1. For children ≥3 years of age (a or b):

a. With cognitive impairment:

– Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ, or spatial IQ ≥1.5 SD below the mean)

OR

– Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment, or visual-spatial impairment)

b. With behavioral impairments without cognitive impairment:

– Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)

2. For children <3 y of age:

– Evidence of developmental delay ≥1.5 SD below the mean.

Table 2. The table shows the diagnostic criteria proposed by Hoyme for PFAS[37,39].

II. PFAS – Partial Fetal Alcohol Syndrome

- For children with **documented** prenatal alcohol exposure, a diagnosis of PFAS requires features A and B:
  A. A characteristic pattern of minor facial anomalies including ≥ of the following
    1. Short palpebral fissures (≤10th centile)
    2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
    3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
  B. Neurobehavioral impairment
    1. For children ≥3 years of age (a or b):
      a. With cognitive impairment:
  – Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
  OR
  – Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
      b. With behavioral impairment without cognitive impairment:
  – Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
    2. For children <3 y of age:
  – Evidence of developmental delay ≥1.5 SD below the mean
- For children **without documented** prenatal alcohol exposure, a diagnosis of PFAS requires all features, A-C:
  A. A characteristic pattern of minor facial anomalies including ≥ of the following
    1. Short palpebral fissures (≤10th centile)
    2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
    3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
  B. Growth deficiency or deficient brain growth abnormal morphogenesis or abnormal neurophysiology
    1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if available), or:
    2. Deficient brain growth, abnormal morphogenesis or neurophysiology, including ≥1 of the following:
      a. Head circumference ≤10th percentile
      b. Structural brain anomalies
      c. Recurrent nonfebrile seizures (other causes of seizures having been ruled out)
  C. Neurobehavioral impairments
    1. For children ≥3 years of age (a or b):
      a. With cognitive impairment:
  – Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
  OR
  – Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment, or visual-spatial impairment)
      b. With behavioral impairment without cognitive impairment:
  – Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
    2. For children <3 y of age:
  – Evidence of developmental delay ≥1.5 SD below the mean.

Table 3. The table shows the diagnostic criteria proposed by Hoyme for ARND[37,39].

III. ARND - Alcohol-Related Neurodevelopmental Disorders

Requires features A and B (this diagnosis cannot be made definitively in children <3 y of age):
  A. Documented prenatal alcohol exposure
  B. Neurobehavioral impairment
For children ≥3 y of age (a or b):
    a. With cognitive impairment:
  –Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD)
  OR
  – Cognitive deficit in at least 2 neurobehavioral domains ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
    b. With behavioral impairment without cognitive impairment:
  – Evidence of behavioral deficit in at least 2 domains ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control).

Table 4. The table shows the diagnostic criteria proposed by Hoyme for ARBD[37,39].

IV. ARBD - Alcohol-Related Birth Defects
Requires features A and B: **A. Documented** prenatal alcohol exposure **B.** One or more specific major malformations demonstrated in PAE animal models and human studies: cardiac atrial septal defects, aberrant great vessels, ventricular septal defects, conotruncal heart defects, skeletal radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis, aplastic/hypoplastic/dysplastic kidneys "horseshoe" kidneys/ureteral duplications, eyes strabismus, ptosis, retinal vascular anomalies, optic nerve hypoplasia, conductive hearing loss, neurosensory hearing loss.

In Italy these criteria have always been preferred to other guidelines for greater completeness in making the clinical diagnosis. This is probably also due to the fact that they are very rigid and precise criteria and therefore the risk of underestimating the pathology is reduced compared to other guidelines.

The presence of these features aids clinicians in making a diagnosis of FAS; nevertheless, not all individuals with PAE will exhibit all of these characteristics, and the severity can vary[61,80]. Consequently, healthcare professionals may use terms such as "pFAS" or "ARND" to describe a range of outcomes associated with PAE[31,34,64].

Hence, diagnosis involves both clinical examination and subsequent laboratory testing, also including exploratory diagnostic techniques such as brain magnetic resonance imaging and ultrasound scans of the brain, heart, or kidneys[64,81,82]. Among genetic tests, comparative genomic hybridization on microarrays, or Array-CGH, is recommended to identify DNA anomalies that may underlie various pathologies[30,58,60,83]. In general, the guidelines mentioned above share four common diagnostic criteria: the presence of dysmorphological signs, growth defects, documented exposure to alcohol, and the presence of cognitive/behavioral disorders[21]. What distinguishes the various guidelines is the starting point for data collection. The IOM and Canadian guidelines consider data collection related to dysmorphological signs and alcohol exposure, while the Australian ones are based on information regarding the individual's cognitive and behavioral functioning, supplemented by collecting information on documented exposure to alcohol[39,72,84,85]. Table 5 shows the criteria for defining the alcohol consumption during pregnancy[35,86].

In addition to the international guidelines, the DSM criteria can also be used, which in its fifth edition[87] included FAS within the diagnostic category: Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE)[47,67]. Individuals who meet the criteria for a diagnosis of FASD according to the IOM guidelines may also meet the criteria for ND-PAE[42,88]. Unlike international guidelines, the DSM-5 employs two criteria to establish a diagnosis: disorders of CNS functioning (cognitive and behavioral) and data concerning fetal exposure to alcohol[21,89,90].

Discussion

Diagnosing FAS requires a comprehensive assessment by healthcare professionals, which includes physical examinations, developmental and behavioral evaluations, and obtaining a detailed history of PAE. Early diagnosis and intervention are crucial in providing appropriate support and services for individuals affected by FAS[91,92]. Given the absence of a genetic test, as FASD is of epigenetic origin, and the lack of specific and

Table 5. The table shows the criteria for defining the prenatal alcohol exposure.

Definition of Documented Prenatal Alcohol Exposure
One or more of the following conditions must be present to constitute documented prenatal alcohol exposure during pregnancy (including drinking levels reported by the mother 3 months before she reported pregnancy recognition or a positive pregnancy test documented in the medical record). The information must be obtained from the biological mother or a reliable collateral source (eg, family member, social service agency, or medical record): • ≥6 drinks/wk for ≥2wk during pregnancy • ≥3 drinks per occasion on ≥2 occasions during pregnancy • Documentation of alcohol-related social or legal problems in proximity to (before or during) the index pregnancy (eg, history of citation[s] for driving while intoxicated or history of the treatment of an alcohol-related condition) • Documentation of intoxication during pregnancy by blood, breath, or urine alcohol content testing • Positive testing with established alcohol-exposure biomarker(s) during pregnancy or at birth (eg, analysis of fatty acid ethyl esters, phosphatidyl ethanol, and/or ethyl glucuronide in maternal hair, fingernails, urine, or blood, or placenta, or meconium)[41,93-98] • Increased prenatal risk associated with drinking during pregnancy as assessed by a validated screening tool such as T-ACE (tolerance, annoyance, cut down, eye-opener) or AUDIT (alcohol use disorders identification test)[99]

standardized biomarkers for detecting patients with FASD, diagnosis remains challenging for physicians. Furthermore, the lack of a unique diagnostic guideline also presents challenges in diagnosing FASD. In Italy, the Hoyme guidelines are preferred due to their comprehensiveness, which enhances diagnostic accuracy while minimizing underestimation of the pathology[46,77].

Conclusions

Implementing a uniform global guideline would be highly beneficial in ensuring an adequate and consistent number of diagnoses. This study aimed to provide a comprehensive overview of some of the most commonly used guidelines, with a particular focus on those frequently applied in Italy, such as the guidelines proposed by Hoyme and his collaborators.

While these guidelines currently appear to be the most comprehensive and effective in minimizing diagnostic underestimation, we acknowledge the challenges in establishing global guidelines. Therefore, we recommend that further studies and collaborative efforts are essential to develop at least homogeneous guidelines.

**Interdisciplinary Study Groups:* Sapienza Università di Roma, ISTAT - Istituto nazionale di statistica, AIDEFAD - Associazione Italiana Disordini da Esposizione Fetale ad Alcol e/o Droghe, SITAC - Società italiana per il trattamento dell'alcolismo e delle sue complicanze. SIFASD - Società Italiana Sindrome Feto-Alcolica, ISS - Istituto Superiore di Sanità, SIPPS - Società Italiana di Pediatria Preventiva e Sociale, FIMMG-Lazio - Federazione Italiana dei Medici di Medicina Generale Lazio, SIMPeSV - Società Italiana di Medicina di Prevenzione e degli Stili di Vita, CIPe - Confederazione Italiana Pediatri. Adele Minutillo, Alba Crognale, Alberto Chiriatti, Alberto Spalice, Andrea Liberti, Angelo Selicorni, Antonella Polimeni, Antonio Greco, Arianna Barzacchi, Camilla Di Dio, Duccio Cordelli, Francesca Fanfarillo, Francesca Tarani, Giovanni Corsello, Lina Corbi, Luca Cavalcanti, Lucia Leonardi, Camilla Perna, Lucia Ruggieri, Luigi Meucci, Marco Lucarelli, Maria Grazia Piccioni, Maria Pia Graziani, Mario Vitali, Marisa Patrizia Messina, Martina Derme, Nunzia La Maida, Patrizia Riscica, Sabrina Venditti, Sergio Terracina, Serafino Zangaro, Pier Luigi Bartoletti, Silvia Francati, Simona Pichini, Stefania Bazzo, Stefania Pipitone.

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Corresponding author:
Luigi Tarani
E-mail: luigi.tarani@uniroma1.it