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Italian Guidelines for the diagnosis and treatment of Fetal Alcohol Spectrum Disorders: structural abnormalities

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Summary. Fetal Alcohol Spectrum Disorders (FASD) encompass a range of conditions caused by prenatal alcohol consumption, leading to physical, behavioral, and learning challenges. It is a significant cause of preventable mental disability, with a prevalence rate of 7.7 cases per 1,000 individuals in the Western world. FASD includes various categories such as alcohol-related neurodevelopmental disorders (ARND), alcohol-related birth defects (ARBD), partial fetal alcohol syndrome (pFAS), and FAS. Mortality is primarily linked to external causes and individuals with FAS may have a projected lifespan of around 34 years. This review highlights the key features of FASD, including neurological impact, behavioral abnormalities, placental and congenital malformations, organic abnormalities, and hormonal and immune disruption. Additionally, potential therapeutic approaches for FASD are briefly discussed based on the different manifestations. Prevention remains the most effective strategy to reduce its incidence, although the general population's understanding of this topic is currently insufficient. Timely diagnosis and intervention are crucial as they can significantly enhance outcomes through appropriate support and management strategies. Increasing awareness among citizens about the detrimental effects of alcohol use disorders on newborn health is of utmost importance.

Key words. Alcohol, FAS, FASD, malformations, neurobehavior, therapy.

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

Riassunto. I disturbi dello spettro feto-alcolico (FASD) comprendono una serie di condizioni causate dal consumo prenatale di alcol, che porta a sfide fisiche, comportamentali e di apprendimento. È una causa significativa di disabilità mentale prevenibile, con un tasso di prevalenza di 7,7 casi ogni 1.000 individui nel mondo occidentale. La FASD comprende varie categorie come i disturbi dello sviluppo neurologico legati all'alcol (ARND), i difetti congeniti legati all'alcol (ARBD), la sindrome alcolica fetale parziale (pFAS) e la FAS. La mortalità è legata principalmente a cause esterne, e gli individui affetti da FAS possono avere una durata di vita media di circa 34 anni. Questa revisione evidenzia le caratteristiche principali della FASD, tra cui l'impatto neurologico, le anomalie comportamentali, le malformazioni placentari e congenite, le anomalie organiche e i disturbi ormonali e immunitari. Inoltre, i potenziali approcci terapeutici per la FASD vengono brevemente discussi in base alle diverse manifestazioni. La prevenzione rimane la strategia più efficace per ridurne l'incidenza, anche se la comprensione di questo argomento da parte della popolazione generale è attualmente insufficiente. La diagnosi e l'intervento tempestivi sono fondamentali in quanto possono migliorare significativamente i risultati attraverso strategie di supporto e gestione adeguate. È di primaria importanza aumentare la consapevolezza tra i cittadini sugli effetti dannosi dei disturbi legati al consumo di alcol sulla salute dei neonati.

Parole chiave. Alcol, FAS, FASD, malformazioni, neurobiologia del comportamento, terapia.

Introduction

Fetal Alcohol Spectrum Disorders (FASD) refer to a variety of presentations and disabilities that occur in individuals whose mothers consumed alcohol during pregnancy[1]. In the general population it has been estimated a prevalence of 7.7 cases per 1,000 individuals[2-4]. The range of associated conditions include various effects, such as physical, behavioral, and learning problems. FASD encompass several categories of disease identified by the Institute of Medicine (IOM)[5]. These categories include alcohol-related neurodevelopmental disorders (ARND), alcohol-related birth defects (ARBD), partial fetal alcohol syndrome (pFAS), and the most severe manifestation FAS[2,6]. The main structural disfunctions associated with FASD are shown in figure 1.

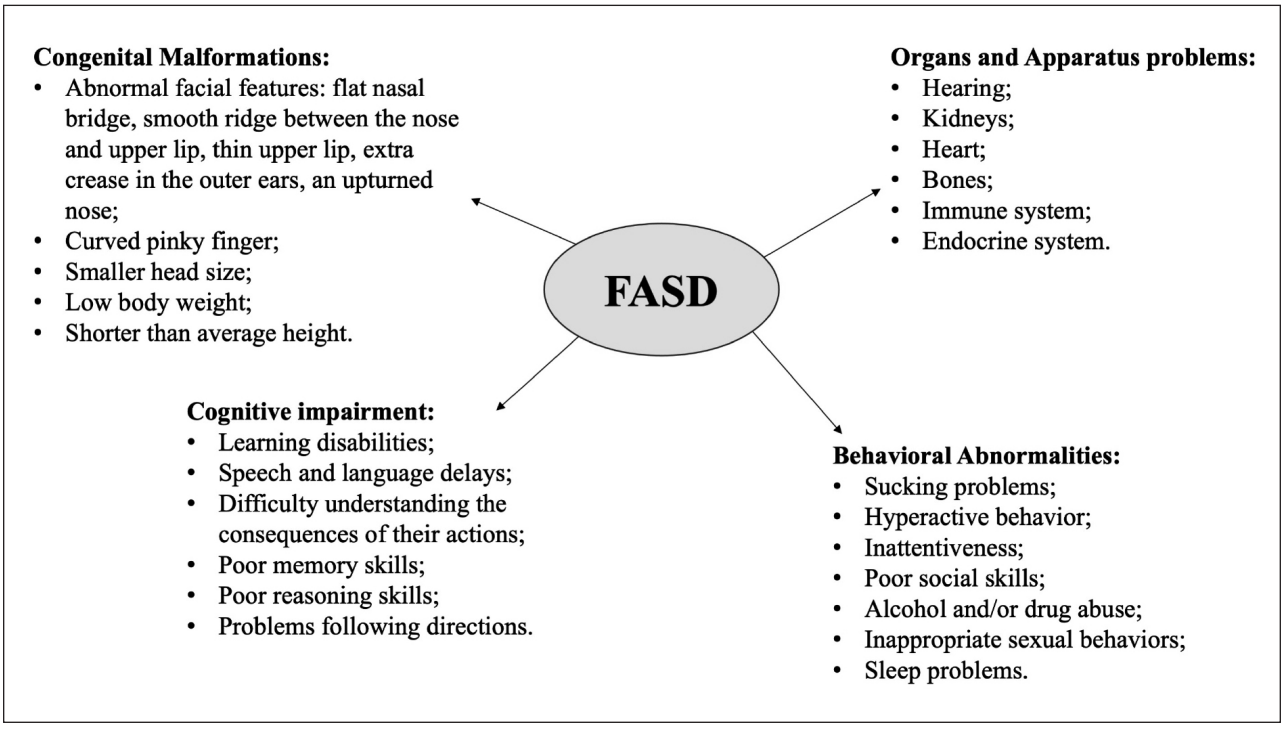

Figure 1. Fetal alcohol spectrum disorders common clinical features.

The projected lifespan for individuals with FAS is approximately 34 years (with a 95% confidence range of 31 to 37 years); the primary contributors to mortality are referred to "external causes" (43%), that comprise suicide (15%), accidents (14%), and fatalities involving illegal drugs abuse or alcohol poisoning (7%) and other factors (7%)[7]. Alcohol interferes with the development of cells and tissues in the fetus. It disrupts the process of cell division and differentiation, leading to abnormal growth and development of various organs, especially the brain[8-10] determining also behavioral changes and impaired learning and memory abilities[11-14]. Alcohol crosses the placenta easily, exposing the fetus to the same concentration of alcohol as the mother, disrupting baby's development[2,15,16]. The timing, amount, and pattern of alcohol consumption during pregnancy can influence the severity of FASD; the early stages of pregnancy are particularly sensitive, as vital organs, including the brain, rapidly develop during this time. Actually, it has also been suggested that paternal consumption of alcohol before conception triggers epigenetic changes in male sperm potentially linked to paternal FASD, so that male alcohol abuse may also play a major role in these diseases[17]. It's recommended that pregnant women completely abstain from alcohol, to ensure the health and well-being of the developing fetus. Maternal trauma may indirectly contribute also to the risk of having a child diagnosed with FASD[18].

Early diagnosis and intervention can help manage the symptoms and improve the quality of life for individuals affected by FASD[19]. Unfortunately, identifying women at risk has proven to be challenging, while the diagnosis of FASD tends to be overlooked or delayed, and it doesn't receive adequate public acknowledgment[20,21]. This oversight in diagnosing has substantial social and economic repercussions[22]. In fact, individuals affected by FASD might face challenges in education, employment, and social interactions, leading to increased dependency on social services and healthcare systems. Aim of this work is to report updated evidence on the structural abnormalities induced by FASD.

FASD and structural abnormalities

Neurological impact and behavioral abnormalities

The fetal brain is particularly susceptible to alcohol exposure mainly because the degree of its vascularization continually increases throughout gestation so that neurological and behavioral abnormalities are common in FASD patients[23]. The detrimental impact of ethanol manifests differently across distinct brain regions, influenced by the dosage and developmental stage during embryonic exposure. It has been demonstrated that during the synaptogenesis period, which spans from the last trimester of pregnancy and first

several years after birth, ethanol has the potential to trigger massive neuronal suicide through its NMDA antagonist and GABAmimetic properties causing brain mass reduction and neurobehavioral disturbances associated with the FASD[24]. Consequences encompass microcephaly, cortical irregularities marked by decreased gyrification, agenesis of corpus callosum or hypoplasia[25]. Research points to the vulnerability of central nervous system (CNS) blood vessels to teratogenic effects of ethanol. These vessels are comprised of specialized endothelial cells, interlinked with astrocytes, pericytes, and microglia, constituting the neurovascular unit crucial for the blood-brain barrier (BBB)[26,27]. The BBB's protective role regulates the passage of substances and medications targeting CNS disorders. Disruptions of the BBB, induced by factors like prenatal alcohol and drug use, congenital infections, or aging, significantly alter its molecular structure and vascular integrity[28-30]. This disruption exacerbates neurodegenerative and neurological conditions. Furthermore, fetal brain epigenetic mutations and reactive oxygen species (ROS)-susceptibility seem to play a major role in causing behavioral changes[31]. An initial study on quantitative electroencephalographic analysis of bioelectrical activity of the brain of children with FASD has just recently been published showing important differences compared to control group including dominance of the alpha rhythm over the beta rhythm and increased theta/beta ratio[32]. In FASD patients, low iron reserves during pregnancy have been associated with a worsening of several features including reduced growth and impaired associative learning[33]. Neuroinflammation plays a major role in neurodegenerative disorders linked to alcohol as various pathways have been studied: α-synuclein, TLR4 signaling cascade, TLR2 and TLR3, IL-10, IL-1β, and TNF-α[34].

Quite interestingly, the fetus of mothers abusing alcohol during pregnancy showed brain changes[35]. Structural changes to the brain include both reductions in gray matter volume and white matter volume, particularly in the prefrontal cortex, gray matter microstructure, thinning of the corpus callosum and decreased cerebellar volume[36,37]. Careful ultrasound analyses revealed that the fetuses of women abusing alcohol during gestation had significantly longer interorbital distance and also significantly increased frontothalamic distance[35]. In another study, fetus of women abusing alcohol during pregnancy showed significantly larger volumes of the corpus callosum and smaller volumes of the periventricular zone[38,39].

FASD has been associated with greater rates of mental health disorders in middle adulthood as well as various neurological and cognitive impairments[40]. These can include intellectual disabilities, learning difficulties, attention deficits, memory problems, poor executive functioning, and behavioral issues. Alcohol intake during pregnancy and breastfeeding, along with preconceptional paternal alcohol consumption (due to its impact on sperm function), are significant contributors to preventable neurodevelopmental impairments in newborns resulting in substantial cognitive and neurobiological deficits[41,42]. In fact, alcohol affects the developing brain, disrupting the formation of neural pathways and potentially causing structural abnormalities. This can lead to cognitive impairments, learning difficulties, and behavioral problems. such as disrupted school experiences (61%, difficulty with attention, poor memory, speech and language delays), trouble with the law (60%), psychiatric inpatient setting (50%, probably related to the poor reasoning and judgment skills), inappropriate sexual behaviors (49%) and alcohol and/or drug problems (35%)[43].

Furthermore, ethanol also affects the alcoholic intake preference of the offspring so that there is a heritage in the drinking behavior that leads to a pathological loop[44]. Studies found that early diagnosis consents to lead these children to grow in a good, stable environment reducing of 2- to 4-fold the chance of these identified adverse life outcomes[45]. Alcohol exposure during the developmental period affects the production of neurotrophins (NTs) which are associated with various mechanisms, including oxidative stress processes, neuroinflammation, cell death, changes in adult neurogenesis in the hippocampus, alterations in dendritic structure and spine density, vascular development, and behaviors linked to spatial memory, anxiety, and depression[46-48]. These molecules play a major role in steering normal brain development and cellular adaptability. Recent studies revealed that pre-pubertal children affected by FASD exhibit lower serum levels of NGF and BDNF compared to healthy controls[47,49]. This imbalance is also linked to disturbances in the peripheral neuroimmune pathways. Furthermore, as shown in animal models, the modulation of oxidative stress in pregnant women throughout the ingestion of vegetables rich in polyphenols, compounds with strong antioxidant activities, could counteract or limit the damage induced by alcohol drinking[11,50,51].

Congenital malformations

Ethanol alters the osteogenic differentiation of amniotic fluid-derived stem cells[52]. Most children diagnosed with FASD do not exhibit the obvious physical traits seen in severe cases[53]. Nonetheless, lasting neurodevelopmental and behavioral issues persist in the affected children across their lives. Certain facial abnormalities like smaller head size, a thin upper lip, flat nasal bridge, flattened philtrum, extra crease in the outer ears, an upturned nose and smaller eye openings are common in individuals with FASD[5,42]. Poor coordination and curved pinky finger are of-

ten present. FASD can result in growth deficiencies, both in terms of height and weight[54]. This problem is also partially accentuated by the common sleep and sucking problems as a baby. Furthermore, chronic alcohol use can also lead to poor maternal nutrition, which indirectly affects fetal development because of lack of essential nutrients[9,54]. Bone and joint abnormalities might be present in some cases, leading to issues with mobility or skeletal development. Interestingly as it is known that alcohol exposure itself is sufficient to induce retinoic acid deficiency in the embryo, recent studies demonstrated that defects in craniofacial development and microcephaly are further amplified by this deficiency through the altered downstream pathways controlled retinoic acid target genes, including Sonic hedgehog signaling[55,56]. As such, it has been demonstrated that ethanol-induced developmental defects can be ameliorated by increasing the levels of retinol, retinaldehyde, or retinaldehyde dehydrogenase[57].

Other organic abnormalities

Vision or hearing problems are common in children with FASD. Common ophthalmological abnormalities are subnormal visual acuity (VA), optic nerve hypoplasia (ONH), retinal vascular malformations, visual perception problems (VPPs), refractive errors, strabismus, short palpebral fissures, ptosis, epicanthus and abnormally increased intercanthal distance (ICD)[58-60]. Recently it has been suggested the FASD Eye Code as a new complementary ophthalmological diagnostic tool to assist in diagnosis and to detect ophthalmological abnormalities in individuals with suspected FASD[61]. It consists of four categories covering four ophthalmological features common in FASD, each category is ranked on a scale from 1 to 4, with 1 indicating normal ophthalmological characteristics and 4 representing a strong presence of ophthalmological anomalies: (a) best-corrected visual acuity (BCVA); (b) refraction; (c) strabismus/binocular function and (d) ocular structural abnormalities. A FASD Eye Code cut-off total score of ≥9 showed high specificity (98%) for FASD versus healthy controls, with a sensitivity of 57%[62]. Among the FASDs, FAS is also associated with four main of hearing disorders: developmentally delayed auditory function, sensorineural hearing loss, intermittent conductive hearing loss due to recurrent serous otitis media, and central hearing loss[63]. Actually, listening difficulties in the absence of hearing loss are prevalent[64]. Furthermore, speech and language pathologies also are common in FASD patients so the early identification and treatment should improve these problems[65].

Even though literature is in partially controversy, heart defects (especially septal) and abnormalities in the structure and function of the heart seem to occur more frequently in these patients, leading to cardiovascular issues[66-69]. In this regard, a recent study suggested that glutathione supplementation may be useful to inhibit effects of prenatal alcohol exposure (PAE) by improving survival, reducing the incidence of morphological defects, and preventing global hypomethylation of DNA in heart tissues[70]. In mice, it has been demonstrated how paternal prenatal alcohol consumption is related to reduced weight of heart, kidney, and ventral prostate[71].

An increased incidence of renal and urinary tract anomalies as well as decreased kidney size was registered among individuals with FASD, but no altered kidney function or higher risk of hypertension have been observed[72]. In this case the teratogenic effects of alcohol on kidney development, especially the reduced ureteric branching morphogenesis and glomerular development, could be ameliorated through treatment with retinoic acid[73].

PAE can also affect the liver and gastrointestinal tract, potentially leading to structural abnormalities or functional impairments[74]. Furthermore, problems with digestion or absorption of nutrients are common in these subjects. Various supplements and therapeutic approaches have been tested but no major breakthroughs have been made[75].

Hormonal and immune disruptions

Alcohol exposure during pregnancy can interfere with the balance of hormones crucial for fetal development, affecting organs growth and function[76]. Alcohol-induced endocrine imbalances may contribute to the etiology of FAS. Further proof of the possible metabolic/endocrine disruption in FASD is the higher rate of overweight and obesity found both in affected children and adolescents[77]. This is even more significant if we take notice of the high prevalence of low birth weight[78]. Most of the hormones and metabolites analyzed to disclose the hormonal regulation of appetite in patients with FASD unfortunately brought inconclusive results[79]. Although fatty acids metabolic measurements are not affected by alcohol exposure, their presence has been shown to alter gut microbiota[80]. NTs altered levels may play a role in the imbalance of the neuroendocrine system and the resulting neurobehavioral effects associated with FASD[81]. In mice, prenatal alcohol abuse can alter the levels of norepinephrine in male offspring, as well as reduce 5-Hydroxytryptamine levels in the cerebrum and increase Met-enkephalin levels in all brain regions[82]. PAE alters maternal-placental-fetal programming of the fetal hypothalamic-pituitary-adrenal (HPA) axis reducing its activity[83].

The HPA axis alteration as well as the hormonal dysfunction can lead to an abnormal activation of the autonomic nervous system resulting in maladaptive

behavioral reactivity later in life[84]. Alcohol consumption during pregnancy causes an increase of maternal glucocorticoids by dysregulating corticotropin-releasing-hormone (CRH) promoter activity (higher CHR expression in hypothalamus, amygdala and hippocampus) by interfering with the negative glucocorticoid response element (nGRE) leading to detrimental exposure levels to the fetus[85]. Higher levels of glucocorticoid exposure due to stress or alcohol, especially in presence of proinflammatory immune-related factors, further influence the maternal and fetal HPA axis responsivity[86]. Alterations in immune competence and increased vulnerability of ethanol-exposed offspring to the immunosuppressive effects of stress may be one of the long-term consequences of fetal HPA programming[87]. Furthermore, prenatal exposure to alcohol has the potential to trigger activation of the maternal immune system, disrupting the delicate balance of cytokines during pregnancy consequently impacting on the developing immune system of the fetus both directly by alcohol exposure and indirectly by the activation of the maternal immune system[88,89].

Alcohol exposure may lead to modifications in epigenetic mechanisms (DNA methylation, histone modification, microRNAs expression) that are believed to play a crucial role as underlying mechanisms driving long-term impairments in the immune function of offspring and alterations in the neuroimmune system (microglial activation and changes in central cytokines)[90]. Indeed, FASD present decreased eosinophil and neutrophil cell counts and reduced leukocyte response to mitogens, associated with a higher incidence of major and minor infections (including recurrent otitis media, upper respiratory tract infections, urinary tract infections, sepsis, pneumonia, and acute gastroenteritis)[91-94]. Researchers demonstrated that the newborns small for gestational age were three times more likely to have a neonatal infection if their mothers drank more than seven drinks per week during pregnancy[95].

Placenta Abnormalities

Placental abnormalities can encompass various conditions, affecting this organ that develops during pregnancy to provide oxygen and nutrients to the growing fetus. Complications can include restricted fetal growth, premature birth, and in severe cases, fetal distress, or stillbirth. The role of placenta on the fetal neurodevelopment is so significant that neuroplacentology has emerged as a new field of research, focusing on the role of the placenta in fetal brain development[96].

There is evidence suggesting that alcohol consumption during pregnancy can contribute to placental abnormalities. Alcohol may disrupt the formation and functioning of the placenta, leading to structural changes or impairments in its ability to provide necessary nutrients and oxygen to the fetus. Recent studies found prenatal alcohol-related epigenetic changes in imprinted genes in placental and brain tissue, with altered expression and methylation[97]. These disruptions can contribute to various placental abnormalities such as placenta previa, placental abruption, or abnormalities in placental attachment. The placental dysfunction caused by alcohol might lead to inadequate nutrient transfer, oxygen deprivation, and other developmental issues that contribute to the spectrum of disorders seen in FASD. Particularly important seems to be the presence of ROS which alter placental function and are associated with both alcohol intake and FASD etiology[98]. Maternal alcohol consumption leads to downstream increases in placenta-derived proinflammatory factors (NF-κB, IL-1β, TNF-α) released by brain glial cells, decidual macrophage and NK immune cells stimulated by the activation of toll-like receptor 4 (TLR4), worsening the scenario[99]. Moreover, there is a 5-7-fold increase risk of chorioamnionitis in adolescents under 18 years of age that use tobacco and alcohol during pregnancy[96,100].

As emphasized by the recent first transcriptomic "placenta-cortex" signature of the effects of PAE on fetal angiogenesis, prenatal alcohol exposure causes an unbalance of several ligands and/or receptors involved in the control of angiogenesis including placental growth factor (PlGF)[101,102]. In particular, down-regulation of PlGF in placenta due to alcohol exposure causes a marked disorganization of the cortical vasculature of the fetus affecting placenta-cortex communication (especially angiogenic interactions) and causing fetal brain alterations[102,103]. A recent study suggested that PAE may inhibit serotonin transporter (SERT) expression while simultaneously promoting increased tryptophan hydroxylase (TPH1) protein expression in human placenta resulting in increased levels of serotonin (5-HT) in fetal circulation which can affect neurodevelopment[104]. A recent study demonstrated that heavy alcohol exposure during pregnancy can influence the proportion of Hofbauer cells (fetal placental villi macrophages) and enhance inflammatory genes expression[105].

Actually, paternal preconceptional alcohol exposures also plays a role as it can induce dose-dependent increases in the placental labyrinth layer, placental hypertrophy and it impairs gene expression in both mitochondrial-encoded and imprinted genes[106].

Therapeutic approaches for FASD malformations

The treatment options for FASD at the moment include prenatal administration of antioxidant food

supplements, folic acid, choline, neuroactive peptides, and neurotrophic growth factors[107]. In particular, studies support the potential proactive maternal nutritional intervention to minimize FASD progression[54,108]. Interestingly, several studies conducted on rodent models found a correlation between prenatal alcohol consumption associated with FASD and alterations in NTs, implying that these proteins might function as neuroprotective molecules capable of counteracting the detrimental effects of PAE[109]. These findings suggest that new therapeutic targets can be explored, and new approaches could be brought to light soon. As epigenetic changes are potentially reversible through pharmaceutical interventions, it has been suggested an opportunity to develop drugs targeting specific epigenetic mechanisms involved in regulating gene expression, which could have significant clinical relevance[47]. Interestingly, recent evidence suggested that alcohol and in general abuse substances can induce splicing alterations through epigenetic modifications which are related to the molecular pathways involved in the interplay with the brain[110].

Additionally, emerging epigenetic tools might be utilized as preventive, diagnostic, and therapeutic markers. Interestingly, dietary soy may provide an economically feasible and accessible means of reducing adverse pregnancy outcomes linked to gestational ethanol exposure[111]. It has been shown to reduce fetal demise, intrauterine growth restriction, craniofacial dysmorphic features, and impairments in placentation linked to gestational alcohol exposure. Its action takes effect abrogating Akt and PRAS40 pathways via insulin and IGF1 receptors signaling, reducing ethanol's inhibitory effects on the placental glycogen cell population (at the junctional zone), on the invasive trophoblast populations (at the implantation site) and on maternal vascular transformation[112].

Discussion and conclusions

FASD is the main preventable cause of mental disability in the western world and it has been amply demonstrated how early diagnosis and management, as well as the identification of women at risk, can strongly reduce the impact of the disease[5,48]. Interestingly, a new field of research, the neuroplacentology, is progressively unearthing the key role of placenta in fetal brain development and in FASD manifestation[96,113]. Most of the children diagnosed with FASD do not exhibit the clear physical traits seen in the more severe cases, but other abnormalities that include vision or hearing problems as well as organ disfunctions (hearth, kidney, liver) are possible[53,54]. Furthermore, immune and hormonal alterations have been associated with significant risk of obesity during adolescence and to an increased susceptibility to infections[86,87]. Actually, early diagnosis is based on the identification of women at risk and on the further evaluations of the clinical and behavioral manifestations described in detail in this manuscript[62]. Recent studies are analyzing new candidate genes as potential biomarkers for alcohol-induced developmental disorders in PAE such as DPPA4, FOXP2, and TACR3[113]. New therapeutic approaches are aiming to influence the drinking behavior of parents in order to prevent the structural abnormalities of individuals born with FASD[114].

Future research should further investigate the genetic predispositions and epigenetic changes that contribute to the development and severity of FASD as well as try to develop and validate new screening tools and biomarkers for early detection in infants and young children. Studies evaluating the effectiveness of different intervention strategies, including behavioral therapies, educational programs, and pharmacological treatments are needed.

In conclusion the critical topic of lifelong disabilities induced by prenatal alcohol consumption is quite challenging at the individual, social, economic, and familial levels. Alcohol abuse is a dangerous condition that causes health damage not only to the parents but also to their offspring, showing sometimes well recognized and sometimes nuanced features. A vast amount of data has been published on FASD, but many aspects remain still unclear. A lot still needs to be done about the early management and prevention.

**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, Antonella Polimeni, Antonio Greco, Arianna Barzacchi, Duccio Cordelli, Francesca Tarani, Ginevra Micangeli, Giovanni Corsello, Lina Corbi, Luca Cavalcanti, Lucia Leonardi, Camilla Perna, Lucia Ruggieri, Luigi Meucci, Marco Lucarelli, Maria Pia Graziani, Mario Vitali, Marisa Patrizia Messina, Martina Derme, Michela Menghi, Nunzia La Maida, Pier Luigi Bartoletti, Roberto Paparella, Sabrina Venditti, Serafino Zangaro, Silvia Francati.

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