



Review

Clinical delineation of fetal alcohol spectrum disorders (FASD) in Italian children: Comparison and contrast with other racial/ethnic groups and implications for diagnosis and prevention

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Abstract

In Italy, little is known about the spectrum of adverse fetal effects related to maternal alcohol use during pregnancy. In this paper, we report on the phenotype of Italian children with fetal alcohol spectrum disorders (FASD). These data were gathered as part of a field study assessing the prevalence of FASD in children in an in-school study in a rural area near Rome. The purposes of this paper are: (1) to completely characterize the clinical phenotype of a large cohort of Italian children with FASD; (2) to correlate and contrast the phenotype of this population with that observed in other populations and reported in the medical literature; (3) to discuss the drinking habits of Italian women, before, during and after pregnancy; and (4) to suggest mechanisms for intervention and prevention of FASD based on data gathered from this study.

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Keywords: Fetal alcohol syndrome; Fetal alcohol spectrum disorders; Dysmorphic features; Maternal drinking; Prevention

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1. Introduction

The adverse effects of alcohol on the developing human comprise a continuum of structural anomalies and behavioral and neurocognitive disabilities, most accurately termed fetal alcohol spectrum disorders (FASD). Fetal alcohol syndrome (FAS), or FASD of any kind, has never before been researched from a population-based perspective in a western European population. The NIAAA recently has funded and coordinated an international consortium of projects (CIFASD) aimed at more complete characterization of the teratogenic spectrum of alcohol. The selection of Italy as one of the project sites resulted in the opportunity to carry out an in-school prevalence study in a rural area in the Lazio region. To make the results comparable, the design of the Italian study was identical to that employed in previous NIAAA-funded epidemiological studies in other countries, primarily South Africa.

Lazio is close to Rome and is characterized by small towns and villages. In Italy, drinking habits are distinctive, since binge drinking is rare (except among young people and mostly in metropolitan areas). In rural areas, daily consumption of “moderate” or slightly increased amounts of wine, always with meals, is so widespread that abstainers are very rare. No differences between males and females have been described. This Italian drinking pattern makes FASD prevention very difficult, since in the case of unintended pregnancy, women continue drinking for the first weeks of pregnancy at least. Thus, this drinking pattern allowed for an opportunity to evaluate the effects of daily “moderate” drinking on the prevalence of FASD.

The extent of drinking behavior during pregnancy in Italy was confirmed by a transverse study performed by our group in Rome in 2003. Drinking habits were investigated in 122 pregnant women by a semi-structured interview: 62.1% of the women drank alcohol prior to pregnancy and 52.6% during pregnancy; thus, only 10% of women quit drinking when pregnant. While 68.4% of women reduced or quit smoking, only 21.5% reduced or quit drinking. 11.7% of pregnant women in this study drank more than 7 drinks per week. Moreover, 2 women started drinking alcohol during pregnancy, probably because of popular and widespread ideas about the safety, and even benevolent effects, of moderate alcohol consumption during pregnancy in Italy. For example, several years ago, beer drinking was widely considered a lactation-enhancer by the general public, and this idea is still

prevalent, mostly among those with lower levels of education.

The purpose of this report is to: (1) present historical and morphometric data on the children enrolled in the study, thereby more completely delineating the clinical spectrum of FASD in Italian children; (2) compare these characteristics to those of affected children of other racial/ethnic groups previously reported in the medical literature; (3) discuss the drinking habits of Italian women, before, during, and after pregnancy; and (4) suggest mechanisms for intervention and prevention of FASD based on the data presented.

1.1. Difficulties in defining and diagnosing the continuum of FASD

Historically, multiple terms have been used to describe the continuum of adverse effects that result from prenatal exposure to alcohol, including fetal alcohol effects (FAE), alcohol-related birth defects (ARBD), alcohol-related neurodevelopment disorder (ARND), and, more recently, FASD (Rosett, 1980; Sokol et al., 1989; Aase et al., 1995; Stratton et al., 1996). In April 2004, the National Organization on FAS (NOFAS) convened a meeting of representatives from three federal agencies in the USA (the National Institutes of Health [NIH], Centers for Disease Control and Prevention [CDC], and the Substance Abuse and Mental Health Services Administration [SAMHSA]) and investigators with expertise in the field to develop a consensus definition of FASD. The resulting definition, which is used in this report, defined FASD as the range of effects that can occur in a person whose mother drank alcohol during pregnancy, including physical, mental, behavioral, and learning disabilities, with possible lifelong implications. As this definition implies, multiple diagnostic categories (e.g., FAS, ARND, and ARBD) are subsumed under the term FASD.

A number of researchers have attempted to define diagnostic criteria for specific clinical categories within FASD. Those set forth by the Institute of Medicine (IOM) in 1996 characterize the spectrum most broadly (Institute of Medicine, 1996); however, the IOM report did not define the specific clinical algorithms necessary for making these diagnoses. Clarifications of the IOM criteria recently have been published, with the aim of providing a diagnostic guide easily applied in a clinical practice, thereby leading to enhanced precision of clinical and population based

research in FASD (Hoyme et al., 2005). These revised criteria are currently being used in a large multicenter study on FASD, including this study.

1.2. Relevant literature on FASD and maternal drinking in Italy: preliminary delineation of FASD phenotypes

Prior to 1978, only a few case reports of children with FAS born to Italian mothers had been published. Signs and symptoms included: postnatal growth deficiency, microcephaly, hypoplasia of the corpus callosum, hyperactivity, and low IQ; these features did not differ significantly from those of affected children diagnosed in other countries. Only 24 cases of FAS in Italy were found in a careful review of the Italian literature (May et al., 2006; Scianaro et al., 1978; Moretti and Montali, 1982; Calvani et al., 1985a,b; Lazzaroni et al., 1992; Scotto et al., 1993; Parazzini et al., 1996; Rocella and Testa, 2003).

Conflicting results have been reported in the few Italian studies about the effects of prenatal exposure to alcohol. In some studies, adverse effects have been reported, such as spontaneous abortion, low birth weight, jaundice, and premature delivery; in other studies, no harmful effects of alcohol drinking during pregnancy have been reported. This last finding is very surprising, since in the study of Primatesta et al. (1993) 9% of women enrolled reported drinking more than 11.5 drinks a week (Primatesta et al., 1993).

Considering the widespread consumption of alcohol during pregnancy in Italy, a nation-wide effort for prevention is needed. Whereas, in the USA the NIH officially advised women that drinking alcohol (any amount) during pregnancy should be avoided, in Italy official pronouncements from governmental health agencies regarding FAS and its prevention are lacking, and the risk of fetal damage related to prenatal alcohol exposure has been under-estimated. The school-based prevalence study in Lazio is the first step toward a basis for such a prevention program, since for the first time in Italy real prevalence statistics will be available.

1.3. Experience in the field

The study design of the in-school prevalence study in Lazio is detailed in the paper by May et al. (2006). In this report, the selection criteria for the subjects enrolled are described only briefly. The children studied represented all children enrolled in first grade at randomly selected schools in Lazio, for whom consent to participate was provided for by parents and/or other guardians. Consent forms were signed and returned by a little over half (51%) of the parents; therefore, exactly half of the children eligible to participate were enrolled. The height, weight, and head circumference (occipitofrontal circumference—OFC) were measured for each child by the local school physicians for the schools in the study. School performance and behavior were assessed by the teachers, by means of the Teacher

Disruptive Behavior Disorder Rating Scale (Italian translation). Also the children's parents were also systematically queried about signs of attention deficit and hyperactivity. The children with impaired growth (height, weight, occipitofrontal head circumference <10% centile) or impaired learning attitude (learning deficit and/or attention and hyperactivity) were advanced to the next tier of screening for dysmorphology assessment. Controls from the same 1st grade classes were chosen via a random number table from all children for whom there were signed consent forms. Control children underwent the same screening and testing simultaneously with the index cases. Maternal alcohol consumption during pregnancy was investigated by a standard interview; the interviewer also obtained family, medical and developmental histories.

1.4. Dysmorphology assessment

Each child who met screening criteria as set forth above (181 subjects and 75 controls) underwent a standardized dysmorphology assessment. Data from the dysmorphology assessment were used to determine potential assignment into an FASD diagnostic category, according to the algorithms set forth in the revised IOM criteria developed in recent years and published by members of the research team (Hoyme et al., 2005). Under these criteria a diagnosis of FAS, with or without confirmation of maternal drinking, requires the following: prenatal and/or postnatal growth retardation (height and/or weight \leq 10th centile), microcephaly (OFC \leq 10th centile) or other evidence of structural brain abnormalities, and specific facial anomalies (at least 2 of the 3 cardinal facial findings, i.e., short palpebral fissures, thin vermilion border of the upper lip, and smooth philtrum). A diagnosis of *partial* FAS (PFAS), with or without confirmed evidence of maternal drinking, requires the facies as above plus one or more of the following features: prenatal and/or postnatal growth retardation, evidence of abnormal brain growth or structure, and evidence of the typical behavioral or cognitive abnormalities associated with FASD. A diagnosis of ARND is considered in children who lack the typical facies and *requires* confirmed prenatal alcohol exposure, structural CNS abnormalities (e.g. microcephaly), and evidence of the complex pattern of behavioral or cognitive abnormalities associated with FASD and which is inconsistent with developmental level and not explained by genetic predisposition, family background, or environment alone (Hoyme et al., 2005).

Each child was examined by two teams of dysmorphologists working blinded to any history or knowledge of the child and family. Palpebral fissure measurements were obtained using a rigid ruler, marked in millimeters, with the examiner directly seated in front of the subject, recording the distance from the medial canthus to the lateral canthus. The morphology of each subject's upper lip and philtrum was scored utilizing the lip philtrum guide, developed by Astley and Clarren (2000). A physical examination was

performed to assess major and minor anomalies, each anomaly carrying a prescribed weight. All children were then given a total dysmorphology score (the sum of all related individual anomalies) and were assigned to one of the following categories: an FASD diagnosis (according to the revised IOM criteria for FASD as outlined above), another diagnosis (not alcohol related), or not FASD.

2. Results

2.1. Demographic characteristics

The sample was well matched in terms of sex balance and age: 51% of all subjects were male and the mean age was 80 months (6.7 years). Prevalence data will not be presented in this report (see detailed data in the paper by May et al., 2006).

2.2. Growth

With respect to growth, there were significant differences between the children with FASD and controls: height, weight and head circumference (OFC) were depressed in the FASD subjects. Each of these items is a key variable in the diagnosis of FASD (Table 1).

Table 2 compares growth measures in subjects with FASD in Italy, South Africa and Finland.

2.3. Revised IOM diagnostic category assignment

Of the 181 studied children, 22 (12%) received a diagnosis of FASD. Four of those subjects (18%) were

assigned a diagnosis of FAS; 17 (77%) a diagnosis of PFAS; and 1 (5%) a diagnosis of ARND. Fifty percent of children diagnosed as FAS exhibited all 3 facial features: short palpebral fissures, thin vermilion border of the upper lip, and a smooth philtrum; 36% of PFAS children had all 3 facial features.

2.4. Major and minor anomalies

Several minor anomalies differed significantly between the FASD groups and controls: hypoplastic midface, short palpebral fissure length, long philtral length, ptosis, epicanthal folds, anteverted nares, smooth philtrum and thin vermilion border of the upper lip were much more frequently observed in the children with an FASD diagnosis. Other physical anomalies that substantially differentiated the two groups included a railroad track ear configuration, camptodactyly, and alteration of palmar crease(s) in the subjects with FASD. The overall dysmorphology score was significantly different ($p < .001$) for the FASD group (12.5) and controls (3.3). The dysmorphology score is a method of quantifying growth deficiency and dysmorphic features; it is not used in assigning a diagnostic category within FASD (see Table 3).

The dysmorphic features observed in the FASD cohort are similar to those described in studies carried out in other parts of Europe and South Africa: hypoplastic mid facial features were similar, especially the smooth philtrum and

Table 1
Comparing % with deficient height, weight and head circumference in FASD children in Italy

Variable	FASD (n = 22)	Controls (n = 68)	P
OFC (cm)	50.8	51.9	<.001
Weight (kg)	22.0	25.5	<.001
Height (cm)	116.2	121.0	<.001

Table 2
Comparing growth measures in subjects with FASD in Italy, South Africa and Finland

Variables	Italy		WCP ^{a,c}		Finland ^b
	FASD (%)	CONTROL (%)	FASD (%)	FASD (%)	
Height (mean centile) (%)	24	58	<3	21	
Weight (mean centile) (%)	46	80	<3	22	
OFC (mean centile) (%)	20	50	2	16	

^aWCP = Western Cape Province (South Africa).

^bAutii-Ramö et al., 2006.

^cViljoen et al., 2005.

Table 3
Dysmorphology Assessment Scale

Feature	Points
Height 10%	1
Weight 10%	2
Occipitofrontal circumference 10%	3
Inner canthal distance 10%	0
Palpebral fissure length 10%	3
Attention-deficit/hyperactivity disorder	1
Fine motor dysfunction	1
Midfacial hypoplasia	2
"Railroad track" ears	1
Strabismus	0
Ptosis	2
Epicanthal folds (nonracial)	1
Flat nasal bridge	1
Anteverted nares	2
Long philtrum	2
Smooth philtrum	3
Thin vermilion border of upper lip	3
Prognathism	0
Cardiac murmur	0
Cardiac malformation (confirmed)	1
Hypoplastic nails	0
Decreased pronation/supination of elbow	2
Clinodactyly of fifth fingers	1
Camptodactyly	1
"Hockey stick" palmar creases	1
Hirsutism	1
Total possible dysmorphology score	35

Table 4
Comparing % dysmorphic features in FASD children in Italy, South Africa and Finland

Dysmorphic features	Italy		WCP ^{a,c} Finland ^b	
	FASD (%)	CONTROL (%)	FASD (%)	FASD (%)
Smooth philtrum (%)	90.9	10.4	60.9	77
Thin vermilion border (%)	86.4	25.4	50.0	87
Altered palmar creases (%)	45.5	19.4	40.6	21

^aWCP = Western Cape Province (South Africa).

^bAutti-Ramô et al., 2006.

^cViljoen et al., 2005.

Table 5
Comparing total dysmorphology scores in subjects with FASD in Italy, South Africa and Finland

Total dysmorphology scores (DS), mean	
Italy	12.5
WCP	14.0
Finland	16.0

the thin vermilion border of the upper lip (Chavez et al., 1988; Sampson et al., 1997). Evidence of abnormal/deficient fetal hand movement (i.e., altered palmar creases and camptodacty) was also similar to populations studied elsewhere (Table 4). Table 5 compares the overall dysmorphology scores of the FASD group in Italy, South Africa and Finland.

3. Discussion

In this paper, we report on the clinical features of one of the largest cohorts of clinically diagnosed children with FASD described in Europe, although during this ongoing study it has become clear that not all children with FASD were native to the targeted geographic region of Italy and the population screened. One reason for this observation is the low participation rate of the families: only 50% of parents agreed to allow their children to participate. It is unclear why the participation rate was low; however, in Italy pediatric medical care is free, and parents may have seen no reason to submit their children for an additional (and perhaps unnecessary) examination.

3.1. FASD phenotype

Children in Italy who have FASD are similar in many ways to those with FASD elsewhere in the world. Their suppressed growth and development, depressed intellectual functioning and behavior is similar to those described in studies in the USA, other parts of Europe, and South Africa: measures of height, weight, and head circumference were depressed, and hypoplastic mid facial features were

common, especially a smooth philtrum and a thin vermilion border of the upper lip. (Chavez et al., 1988; Little et al., 1990; Lazzaroni et al., 1992; Adnams et al., 2001; Stromland et al., 2005). Comparing Italian children with FASD with affected children from Finland and South Africa, the Italian children displayed less growth deficiency than those in the other groups. The overall dysmorphology score was elevated among children with FASD from all racial and ethnic groups analyzed in this study. However, the total scores (although all were elevated) differed significantly among the groups, with Italian children displaying a significantly lower mean dysmorphology score. The reason for the lower score among Italian children is not clear, although a lesser degree of growth deficiency in Italian children as compared to their South African or Finnish counterparts likely is a major contributing factor. Although the exact reason for this less significant degree of growth deficiency is unclear, it may reflect better nutrition during pregnancy among Italian mothers of children with FASD, lower levels of alcohol consumption during their pregnancies, lower maternal blood alcohol levels because of a pattern of drinking during meals, or differences in genetic susceptibility to FASD accounted for by maternal and/or fetal genotypes (Bonati and Fellin, 1991; Kvigine et al., 2003; May et al., 2006).

3.2. Implications for FASD prevention

Although the number and severity of negative effects of prenatal exposure to alcohol on the psycho-physical development of the child can range from subtle to serious, such effects are always lifelong, and effective treatment is unavailable (Abel, 1996). Thus, FAS prevention is a worthwhile task. In Italy, the risk for FAS is increased by the widespread pattern of alcohol drinking in the entire population, including a large number of reproductive women who drink moderately during meals, even when pregnant. In addition, the population is poorly aware of and consistently underestimates the risk for FASD.

This first study in a large group of Italian children was a significant step toward FAS prevention. Moreover, awareness of the problem among teachers and health workers (physicians, psychologists and allied health staff) employed in the study and the children's families was heightened. It is anticipated that information regarding FASD, its diagnosis and prevention will be disseminated to the local population.

The data from the interviews of the mothers may be very helpful for understanding the drinking habits of Italian women, prior to, during and after pregnancy. Nearly all of them were current drinkers at the time of the study. Surprisingly, 100% of mothers of the control children were drinkers, while only 90% of FASD mothers admitted to current alcohol consumption, leading the interviewers to question the veracity of their answers. An alternative explanation may be that some of the FASD mothers were

alcoholics who drank during the index pregnancy, later becoming abstinent. Two-thirds of the women admitted to drinking during pregnancy, with no difference in percentage reported between mothers of children with FASD and mothers of controls. These data led the interviewers to question the veracity of these answers to an even greater extent.

This study led to development of an increased local diagnostic capacity for FASD, since local Italian health care professionals were given extensive hands-on training in the diagnostic method by the American experts. Such professional training is not only a crucial step for the children's diagnosis and prevention, but it is also an essential first step toward prevention, since awareness of the problem will be further increased by these professionals educating their peers and colleagues. Moreover, the parents of children with FASD will be informed of the risks of prenatal exposure to alcohol in future pregnancies, thereby potentially decreasing the total number of future children born with FASD in the local community. This is particularly important since the probability of FASD is markedly increased in subsequent offspring of women who have had one child with FASD.

More relevant is the opportunity to intervene and help children with FASD, as was the case for two children evaluated in this screening. As further discussed, children with special needs should be included in the regular classroom, if possible. In Italy, the individual needs of a child with FASD in a regular classroom may be addressed by a personal teacher (teacher's aide), cooperating with the regular classroom teacher. The Medicina Scolastica (school medicine) Service accepted the recommendations from the FASD diagnostic team, and both the children were assigned a personal teacher. The detection and formal diagnosis of FAS and FASD cases is the obligatory first step toward the design of a carefully structured environment for the affected child, in order to maximize his or her potential.

An interesting side benefit of this study was the improvement of the teachers' and parents' awareness of behavioral and learning problems of the children in the study. In the first year of the study, 11.4% of children were diagnosed with attention deficit, 13.4% with hyperactivity, and 13.4% with specific learning disabilities. The diagnosis was not confirmed in all the cases, but in most cases this information led to a modification of the child's school environment and to an improvement of the parents' attitudes toward and care of their child's problems. Indeed, the teachers found that improved parental and school support of their evaluation of children's behavior could improve their own attitudes toward problematic children.

All information obtained in this study is available from the Territorial Health Services participating in the study (except for the privacy-restricted information), and may be used for the implementation of further projects in the field. The Italian institutions and services participating in the study have acquired new expertise and insights into a

heretofore poorly defined problem, and this information will be shared with their entire organizations. Thus, the improved awareness and knowledge of the effects of prenatal exposure to alcohol are more far-reaching than the present results described here.

3.3. Suggestions for further action

Awareness of the problems related to prenatal exposure to alcohol may be increased only by a careful assessment of FAS and FASD risk in our country (currently unknown) and by a nation-wide public education campaign, with widespread media support, targeted at the promotion of the health of pregnant women and unborn children. Women of childbearing age, not pregnant and not on contraceptive treatment, should be advised to drink no more than seven drinks per week and no more than three drinks on any one occasion. All women should be advised that a safe level of drinking during pregnancy has not been determined, and that abstinence during pregnancy is the safest course. This is a difficult task in Italy, since Italy is a major international wine producer, and all campaigns aimed at a reduction of wine drinking (at any rate and in any population subsets) are strongly opposed by the lobbies of wine growers and wine producers.

In Italy, clinicians and psychologists should be advised of the need to take a thorough history to determine alcohol use in all women of childbearing age. During pregnancy, obtaining a careful drinking history is mandatory. Screening tests to detect at risk pregnancies, such as T-ACE (Tolerance, Annoyance, Cut down, Eye-opener) may be helpful (King, 1986; Sokol and Clarren, 1989; Kaskutas and Graves, 2000; Sobell et al., 2001; Jacobson et al., 2002). Also the assessment of common markers of alcoholism (γ -GT, MCV, GOT/GPT ratio, CDT) in at risk mothers may be useful.

A crucial step in the prevention of FAS/FASD is the avoidance of unplanned pregnancies in heavy-drinking women, since many such women continue to drink heavily well into their pregnancies, not knowing they are pregnant. Brain damage may result from alcohol exposure in any trimester, even before an initial positive pregnancy test. Unfortunately, at-risk sexual intercourse is common in alcoholics, and unintended pregnancies are frequent in female alcoholics. Prenatal counseling is considered a mainstay of FASD prevention, as pregnant women should be strongly advised not to drink during pregnancy. Unfortunately, in the case of an unplanned pregnancy, if women have counseling *after* they know they are pregnant, they already may have drunk an amount of alcohol associated with teratogenic effects in the fetus. Thus, pre-conception counseling of women of childbearing age who are at risk for an alcohol-exposed pregnancy and who are not using effective contraception has been demonstrated to be a promising method of prevention, and should be made available by the National Health Service. Some studies in animal models suggest that the administration of

antioxidants, free-radical scavengers and novel peptides to pregnant women unable or unwilling to quit drinking may reduce fetal damage; however, research in humans is lacking.

Early diagnosis of FASD may reduce the impact of the associated lifelong disabilities (Coles et al., 2000). The diagnosis of FASD at birth and in early infancy and childhood is difficult; however, a careful examination by a specially trained pediatrician, clinical geneticist, or dysmorphologist may be helpful. Also the assessment of some biological markers in the newborn may be a useful diagnostic adjunct (Klein et al., 2002). At present, the assessment of fatty acid ethyl esters (FAEE) in meconium seems the most useful, and the availability of this test should be improved. In the long run, once a FASD diagnosis is made, a safe, well-structured and comfortable environment for the child is needed, as well as an individualized teaching program.

Unfortunately, among Italian Medical Faculties teaching about FASD (as well as alcoholism) is poor, and depends mainly on the personal knowledge and sensitivity of single teachers. Guidelines for diagnosing FAS and other negative birth outcomes resulting from prenatal exposure to alcohol should be developed and incorporated into university curricula for students in medicine, nursing, and psychology. In addition, continuing professional training about FASD for general practitioners is needed.

Thus, FAS prevention and maternal/infant health promotion should become major public health targets in Italy, since no effective treatment is at present available for the effects of prenatal exposure to alcohol. In addition the professional training of skilled health professionals in all aspects of FASD diagnosis, intervention, and prevention is crucial and should be implemented in order to begin to address this long-ignored societal problem, not only in Italy but worldwide, wherever women drink alcohol while pregnant.

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References

- Aase, J.M., Jones, K.L., Clarren, S.K., 1995. Do we need the term "FAE"? *Pediatrics* 95, 428–430.
- Abel, E.L., 1996. *Fetal Alcohol Syndrome From Mechanism To Prevention*. CRC Press, Boca Raton, FL.
- Adnams, C.M., Kodituwakku, P.W., Hay, A., Moltano, C.D., Viljoen, D., May, P.A., 2001. Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcoholism: Clinical and Experimental Research* 25, 557–562.
- Astley, S.J., Clarren, S.K., 2000. Diagnosing the full spectrum of fetal alcohol exposed individuals: introducing the 4-digit diagnostic code. *Alcohol and Alcoholism* 35, 400–410.
- Autii-Ramö, I., Fagerlund, Å., Ervalahati, N., Loimu, L., Korkman, M., Hoyme, H.E., 2006. Fetal alcohol spectrum disorders in Finland: clinical delineation of 77 older children and adolescents. *American Journal of Medical Genetics* 140A, 137–143.
- Bonati, M., Fellin, G., 1991. Changes in smoking and drinking behaviour before and during pregnancy in Italian mothers: implications for public health intervention. *International Journal of Epidemiology* 20, 927–932.
- Calvani, M., Ghirelli, D., Calvani, M., 1985a. Fetal alcohol syndrome. *Recent Progress in Medicine* 76, 476–486.
- Calvani, M., Ghirelli, D., Calvani, M., Fortuna, C., Lalli, F., Marcolini, P., 1985b. Fetal alcohol syndrome: clinical, metabolic and immunologic follow-up in 14 cases. *Minerva Pediatrica* 37, 77–88.
- Chavez, G.F., Cordero, J.F., Becerra, J.E., 1988. Leading major congenital malformations among minority groups in the United States, 1981–1986. *Morbidity and Mortality Weekly Report* 37, 17–24.
- Coles, C.D., Kable, J.A., Drews-Botsch, C., Falek, A., 2000. Early identification of risk for effects of prenatal alcohol exposure. *Journal of Studies on Alcoholism* 61, 607–616.
- Hoyme, H.E., May, P.A., Kalberg, W.O., Kodituwakku, P., Gossage, J.P., Trujillo, P.M., Buckley, D.G., Miller, J.H., Aragon, A.S., Khaole, N., Viljoen, D.L., Jones, K.L., Robinson, L.K., 2005. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics* 115, 39–47.
- Institute of Medicine: *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. National Academy Press, Washington, D.C., 1996.
- Jacobson, S.W., Chiodo, L.M., Sokol, R.J., Jacobson, J.L., 2002. Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome. *Pediatrics* 109, 815–825.
- Kaskutas, L.A., Graves, K., 2000. An alternative to standard drinks as a measure of alcohol consumption. *Journal of Substance Abuse* 12, 67–78.
- King, M., 1986. At risk drinking among general practice attenders: validation of the CAGE questionnaire. *Psychological Medicine* 16, 213–217.
- Klein, J., Chan, D., Koren, G., 2002. Neonatal hair analysis as a biomarker for in utero alcohol exposure. *Clinical Biochemistry* 347, 2086.
- Kvigne, V.L., Leonardson, G.R., Borzelleca, J., Brock, E., Neff-Smith, M., Welty, T.K., 2003. Characteristics of mothers who have children with fetal alcohol syndrome or some characteristics of fetal alcohol syndrome. *Journal of American Board of Family Practice* 16, 296–303.
- Lazzaroni, F., Bonassi, S., Magnani, M., Puglisi, P., Salomone, P., Pantarotto, F., Mazzeo, P., Cotelessa, G., Norelli, M.T., Santi, F., 1992. Effects of moderate maternal drinking on some neonatal parameters. *Minerva Pediatrica* 44, 511–517.
- Little, B.B., Snell, L.M., Rosenfeld, C.R., Gilstrap, L.C., Gant, N.F., 1990. Failure to recognize fetal alcohol syndrome in newborn infants. *AJDC* 144, 1142–1146.
- May, P.A., Brooke, L.E., Gossage, J.P., Snell, C., Hendricks, L., Croxford, J., Marais, A.S., Viljoen, D.L., 2006. Maternal risk factors for fetal alcohol syndrome in the Western Cape Province of South

- Africa: a population-based study. *American Journal of Public Health*, in press.
- Moretti, M., Montali, S., 1982. Fetal defects caused by the passive consumption of drugs. *Pediatr. Med. Chir.* 4, 481–490.
- Parazzini, F., Chatenoud, L., Benzi, G., Di Cintio, E., Dal Pino, D., Tozzi, L., Fedele, L., 1996. Coffee and alcohol intake, smoking and risk of multiples pregnancy. *Human Reproduction* 11, 2306–2309.
- Primates, P., Del Corno, G., Bonazzi, M.C., Waters, W.E., 1993. Alcohol and pregnancy: an international comparison. *Journal of Public Health Medicine* 15, 69–76.
- Roccella, M., Testa, D., 2003. Fetal alcohol syndrome in developmental age. *Neuropsychiatric aspects. Minerva Pediatrica* 55, 63–74.
- Rosett, H.L., 1980. A clinical perspective of the fetal alcohol syndrome. *Alcoholism: Clinical and Experimental Research* 4, 119–122.
- Sampson, P.D., Streissguth, A.P., Bookstein, F.L., Little, R.E., Clarren, S.K., Dehaene, P., Hanson, J.W., Graham Jr., J.M., 1997. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. *Teratology* 56, 317–326.
- Scianaro, L., Prusek, W., Loiodice, G., 1978. The fetal alcohol syndrome: clinical observations. *Minerva Pediatrica* 30, 1585–1588.
- Scotto, D.T., Venturino, G., Sorrentino, I., Infuso, D., D'Amiano, G., Palmieri, G., 1993. Fetal alcoholic syndrome: a clinical case. *Pediatr. Med. Chir.* 15, 525–529.
- Sobell, L.C., Agrawal, S., Annis, H., Ayala-Velazquez, H., Echeverria, L., Leo, G.I., Rybakowski, J.K., Sandahl, C., Saunders, B., Thomas, S., Zioikowski, M., 2001. Cross-cultural evaluation of two drinking assessment instruments: alcohol timeline followback and inventory of drinking situations. *Substance Use and Misuse* 36, 313–331.
- Sokol, R.J., Clarren, S.K., 1989. Guidelines for use of terminology describing the impact of prenatal alcohol on the offspring. *Alcoholism: Clinical and Experimental Research* 13, 597–598.
- Sokol, R.J., Martier, S.S., Ager, J.W., 1989. The T-ACE questions: practical prenatal detection of risk-drinking. *American Journal of Rics and Gynecology* 1160, 863–886.
- Stratton, K., Howe, C., Battaglia, F.C., 1996. *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. Washington: Institute of Medicine and National Academy Press, New York.
- Stromland, K., Mattson, S.N., Adnams, C.M., Auti-Ramo, I., Riley, E.P., Warren, K.R., 2005. Fetal alcohol spectrum disorders: an international perspective. *Alcoholism: Clinical and Experimental Research* 29 (6), 1121–1126.
- Viljoen, D.L., Gossage, J.P., Adnams, C.M., Jones, K.I., Robinson, L.K., Hoyme, H.E., Snell, C., Khaole, N., Asante, K.K., Findlay, R., Quinton, B., Brooke, L.E., May, P.A., 2005. Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. *Journal of Studies on Alcohol* 66, 593–604.