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Maternal risk factors for fetal alcohol spectrum disorders in a province in Italy☆

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ABSTRACT

Background: Maternal risk factors for fetal alcohol spectrum disorders (FASD) in Italy and Mediterranean cultures need clarification, as there are few studies and most are plagued by inaccurate reporting of antenatal alcohol use.
Methods: Maternal interviews ($n = 905$) were carried out in a population-based study of the prevalence and characteristics of FASD in the Lazio region of Italy which provided data for multivariate case control comparisons and multiple correlation models.
Results: Case control findings from interviews seven years post-partum indicate that mothers of children with FASD are significantly more likely than randomly-selected controls or community mothers to: be shorter; have higher body mass indexes (BMI); be married to a man with legal problems; report more drinking three months pre-pregnancy; engage in more current drinking and drinking alone; and have alcohol problems in her family. Logistic regression analysis of multiple candidate predictors of a FASD diagnosis indicates that alcohol problems in the child's family is the most significant risk factor, making a diagnosis within the continuum of FASD 9 times more likely (95% C.I. = 1.6 to 50.7). Sequential multiple regression analysis of the child's neuropsychological performance also identifies alcohol problems in the child's family as the only significant maternal risk variable ($p < .001$) when controlling for other potential risk factors.
Conclusions: Underreporting of prenatal alcohol use has been demonstrated among Italian and other Mediterranean antenatal samples, and it was suspected in this sample. Nevertheless, several significant maternal risk factors for FASD have been identified.

1. Introduction

Maternal and child risk factors that influence the severity of fetal alcohol spectrum disorders (FASD) can be grouped into factors of: (1) the host (mother's health, age, diet, body mass index (BMI), nutrition, gravidity (No. of pregnancies), and parity (No. of viable births); (2) alcohol exposure to the fetus (by quantity, frequency, and timing of dose); (3) maternal antenatal environment (socio-economic status (SES), prenatal care, social norms; May and Gossage, 2011; May et al., 2014a); and (4) for neurodevelopment, the quality of child's postnatal environment (mother's education,

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cognitive/behavioral stimulation, and nutrition; Gibbs and Forste, 2014; Jacobson et al., 2014; May et al., 2013c). But much of the evidence for specific maternal risk for FASD originates from studies in lower SES subpopulations, and questions remain about maternal risk in middle and upper SES populations where low fertility and better living conditions reduce the above risks (Abel and Hannigan, 1995; Abel and Sokol, 1987; May et al., 2005, 2008a, 2011b, 2013a).

1.1. General maternal risk in Mediterranean studies

In Mediterranean cultures, regular social drinking, generally with meals, is the modal pattern of alcohol consumption among females; but drinking frequency and specific levels of fetal alcohol exposure are not adequately understood. While descriptions of fetal alcohol syndrome (FAS) existed in the Italian literature (Calvani et al., 1985; Moretti and Montali, 1982; Roccella and Testa, 2003; Scianaro et al., 1978; Scotto et al., 1993), early maternal risk studies found little relationship between maternal alcohol use and adverse outcomes (De Nigris et al., 1981; Parazzini et al., 1994, 1996; Primatesta et al., 1993). Prenatal alcohol use and smoking were linked with low birth weight (Lazzaroni et al., 1993); one-third of women delivering in Italian hospitals were daily drinkers, even after recognition of pregnancy (Bonati and Fellin, 1991); and "abusive" and binge drinking were occasionally linked to spontaneous abortion and low birth weight (Cavallo et al., 1995). In Milan, 9% of women reported risky average weekly alcohol use prior to pregnancy and 29% drank daily during pregnancy (Primatesta et al., 1993). These rates are higher than those reported in the United States (Floyd et al., 1999), and comparable to those in Norway (Alvik et al., 2006b). Therefore, recognition of problem prenatal alcohol exposure started slowly in Italy.

Recent studies in Italy and Spain provide further evidence of maternal risk for FASD. In Verona, a study linked small for gestational age babies to women who reported consuming ≥3 drinks per day in each trimester (Chiaffarino et al., 2006). In Rome, antenatal clinic data indicated that 17.7% of women use alcohol during pregnancy and linked use to being unmarried, having had a previous induced abortion, and low parity (De Santis et al., 2011). In Spain, smaller head circumference at birth was associated with alcohol, illegal drug, and tobacco use, and maternal alcohol use was linked to low maternal and paternal education level, net family income, and father's alcohol use (Ortega-Garcia et al., 2012).

1.2. Unreliability of self-reporting measured by biomarkers

Biomarkers provide new ways to assess prenatal drinking. Manich et al. (2012) compared self-reported prenatal alcohol use in Barcelona, Spain, to levels of fatty acid ethyl esters (FAEE) in the meconium of their offspring, and 16% of those reporting no alcohol use were indeed exposing their fetuses to alcohol in pregnancy. In another meconium analysis of FAEE in Barcelona, gestational alcohol use was found in 45% of women (Garcia-Algar et al., 2008). A similar study in seven Italian cities concluded that 7.9% of fetuses were alcohol-exposed, the highest was in Rome (29.4%), and low maternal education and younger age were associated with maternal drinking (Pichini et al., 2012). Using meconium FAEE in three Italian sites and Barcelona, Spain, 11.9% of mothers exposed their fetuses to alcohol. Again, Rome had the highest exposure (22.6%), and those most likely to cause fetal exposure had less education and low SES (Morini et al., 2013). Especially in Rome, women reported drinking regularly before and after pregnancy, yet 65% of Roman women denied drinking during pregnancy, and "the few who admitted consumption, declared just a drink per month [or] per week" (Morini et al., 2013, p. 405). These contradictions between self reported maternal drinking and biomarker evidence led to the conclusion that "…mothers from Mediterranean countries tend to lie or underreport their toxic habits…and questionnaires often result [in] unreliable and useless [information]" (Morini et al., 2013, p. 405).

1.3. Population-based prevalence studies of FASD in Italy

Research into the prevalence and characteristics of FASD among first grade students in the Lazio region of Italy, where Rome is located, revealed a prevalence of FAS of 4 to 12 per 1000, and FASD was estimated to be 2.3% to 6.3% (May et al., 2011a). This is higher than commonly-accepted estimates for mainstream western populations. Complete maternal interview data from the Lazio study are analyzed here to identify specific maternal characteristics that are associated with a child diagnosed with FASD. Given misrepresentation or underreporting by many women, such factors are not easily determined.

2. Methods

2.1. Institute of Medicine (IOM) diagnostic categories of FASD

The major outcome variable in this risk analysis is a child diagnosed with a FASD in the first grade. Children ages 6 and 7 are at an excellent age for accurate diagnosis of FASD, as their cognitive and behavioral development can be tested with discriminating tests and behavioral checklists. Revised diagnostic criteria for FASD of the U.S. Institute of Medicine (IOM; Stratton et al., 1996; Hoyme et al., 2005) were employed. Each child was examined for: (1) physical growth and facial and other dysmorphology, (2) cognitive/behavioral development, and (3) their mothers were interviewed about alcohol use, health, and social risk factors. Also, other known anomalies of genetic and other teratogenic origins were ruled out. Final diagnoses were made by medical geneticists via a formal, data-driven, multi-disciplinary, case conference which carefully considers empirical findings in each of the above three domains (May et al., 2006, 2011a). Because physical traits are most directly and definitively linked with prenatal alcohol exposure (May et al., 2010, 2013c), the diagnosis is primarily driven by dysmorphic physical features (especially 3 cardinal facial features, microcephaly, and specific other minor anomalies). The revised IOM diagnostic guidelines have been utilized and validated in multiple populations (May et al., 2010, 2013b; May et al., 2014b).

IOM diagnoses for FASD are: FAS, PFAS, alcohol-related neurodevelopmental disorder (ARND), alcohol-related birth defects (ARBD; Stratton et al., 1996). Specific criteria for each are described in detail elsewhere (Hoyme et al., 2005). Diagnosis of FAS or PFAS without a confirmed history of alcohol exposure is allowed by revised IOM criteria. In this study, prenatal alcohol use was directly confirmed by the mother's interview in 61% of the cases. Where diagnosis of FAS or PFAS was made without direct maternal confirmation of use, required criteria for FASD dysmorphia were met, poor neurodevelopment was documented from testing, and collateral reports frequently confirmed prenatal alcohol use. Women from middle and upper SES populations in Europe and the USA have demonstrated a reluctance to admit drinking during pregnancy even while reporting alcohol use both before and after the same pregnancy (Morini et al., 2013; Wurst et al., 2008). Diagnosis of the less dysmorphic forms of FASD, such as ARND, is not allowed without direct confirmation of prenatal alcohol use, because neurobehavioral traits alone are not definitive indicators of prenatal alcohol use (May et al., 2013c). Because of these discrepant links to prenatal drinking, we have used both the diagnosis of a FASD, and the isolated data on neurobehavioral outcomes to model the most significant risk factors.

2.2. Overall Lazio study design and sampling

Mothers of first grade students from two health districts of the Lazio region were interviewed. The overall study was a cross-sectional, active ascertainment, case-control design of the prevalence and characteristics of FASD. Forty-three schools were randomly selected from the 68 elementary schools in the districts. Total first grade enrollment in selected schools was 1989 children. Positive consent forms were returned by 49% of the parents. The total sample of children was 976. The 46 children diagnosed with a FASD were significantly different from randomly-selected, normal controls ($n = 116$) on all key indicators of FASD of physical growth and development as reported elsewhere (May et al., 2006a, 2008a, 2011a) and summarized here in Table 3. Eight children had FAS, 36 PFAS, one ARND, and one ARBD. All procedures were approved by the Ethics Committee of the Italian health districts and the University of New Mexico IRB (approval no. 03-089).

2.3. Developmental (IQ, cognitive and behavioral) testing for FASD suspects and controls

In the overall study, children suspected of having, and eventually diagnosed with, a FASD and all randomly-selected control candidates were provided identical physical exams. Neurobehavioral testing was also provided: Rustioni Qualitative