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Alcohol consumption during pregnancy and adverse neurodevelopmental outcomes

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Lack of evidence is not the same as evidence of absence of risk and, in this case, no evidence of harm does not mean evidence of no harm; subsequently, no amount of alcohol during pregnancy can be considered safe based on research evidence. Newborns exposed to maternal alcohol during pregnancy can develop a spectrum of characteristic facial features, impaired neurodevelopment, cognitive and behavioural disabilities, and fetal growth restriction known as fetal alcohol spectrum disorder (FASD), with the most severe form, including specific morphological facial abnormalities, defined as fetal alcohol syndrome (FAS).[1–6] However, most patients with FASD exhibit only a subset of the characteristics of FAS, such as cognitive and behavioural deficits, and, possibly, facial abnormalities.[4] FASD and FAS represent the most recurrent and easily preventable cause of acquired development disabilities in newborns.[2 6] It is a serious problem for the individual and for society; it entails not only human suffering but also loss of productivity, and a high burden of medical and social costs.[5 6]

There are several unsolved questions related to prenatal alcohol exposure and adverse neurodevelopmental outcomes. The true rate of prenatal alcohol consumption in different countries using reliable tools of estimation is unknown. It is recognised that FASD is entirely preventable through alcohol abstinence, but worldwide 30% (60% in certain countries) of pregnant women consume alcohol during pregnancy.[7 8] In Canada, prevalence rates of FAS and FASD have been reported to be 1–3 and 9 per 1000 live births, respectively, higher than the FAS prevalence of 0.5–2.0 per 1000 live infants in the USA.[9 10] Currently, in Europe, there are no systematic data on FAS and FASD prevalence rates, nor on prenatal exposure to ethanol, and only one retrospective study in Italy showed a prevalence of FAS between 3.7 and 7.4 per 1000 births and a prevalence of FASD between 20.3 and 40.5 per 1000 births.[11]

Differences in the prevalence of FASD may be due to different modes of alcohol consumption, namely, binge drinking or lower daily doses (social drinking); different methods employed to identify the deleterious effects of prenatal ethanol exposure based on clinical tests; inaccuracies; non-uniformity of questionnaires; and not using objective biomarkers. Self-reporting by questionnaire has been shown to underestimate alcohol consumption during pregnancy compared to objective biomarkers in alternative biological matrices such as maternal hair or neonatal meconium.[5–7 12]

In many cases, the fetus is exposed to the teratogenic effects of ethanol during the critical period of organogenesis, before pregnancy is confirmed.[6] Although women tend to decrease their alcohol consumption during pregnancy, their actual level of drinking depends to a large extent on their drinking habits prior to conception.[9 10 13] The high prevalence of FASD is not surprising given the significant percentage of pregnant women consuming ethanol; most of them not considering drinking as being dangerous.[4 7 12 14]

Since the evidence of maternal drinking is always a critical pre-requisite for FASD, it is important to objectively assess alcohol consumption in pregnant women, to create a targeted intervention to stop consumption during pregnancy. Most importantly, for an early diagnosis of prenatal exposure and proper follow-up, sensitive and specific biomarkers are needed.[14] In the absence of a totally expressed syndrome, early diagnosis is not easy and can only count on objective biomarkers for established prenatal alcohol exposure.[6 10 12] For this reason, implementation of biochemical neonatal screening for prenatal alcohol exposure could be a good strategy in truly identifying exposed newborns.[12]

Diagnosis of FASD is difficult due to phenotypic variation, specifically because of different patterns of ethanol consumption in each country, and it is often a diagnosis of exclusion.[12 15] Clinicians should also exclude genetic and dysmorphic syndromes that share clinical features with FAS.[10]

Diagnostic criteria for FAS with confirmed maternal alcohol exposure, reported by Canadian guidelines, are: a characteristic pattern of facial anomalies including short palpebral fissures and abnormalities in the premaxillary zone; evidence of growth retardation (low birth weight for gestational age, decelerating weight over time not due to other identified causes, or disproportionately low weight to height ratio); and evidence of central nervous system abnormalities (decreased cranial size at birth, structural brain abnormalities, impaired motor skills, neurosensory hearing loss, poor tandem gait or poor hand–eye coordination).[16]

Recognising clinical features of FAS is not simple and diagnosis should be supported by an established history of significant prenatal alcohol exposure. Until now, the only mode to obtain this information has been by interviewing the mother or by using a standardised questionnaire. However, women tend to under-report the frequency of alcohol consumption and/or refuse to reveal their gestational alcohol use because of guilt or fear of stigma.[6 10 12]

With the goal of clearly demonstrating the deleterious effects of prenatal alcohol exposure on neurodevelopment, it will be very important to complete the follow-up of exposed newborns and young children. Epidemiological data indicating a high prevalence of prenatal alcohol exposure and FASD in children in Russian orphanages has been published. It suggests that the high prevalence of mental health, behavioural and learning problems of adopted children from East European countries could be due to undiagnosed FASD, and not only due to institutionalisation in orphanages.[17–19] There is an urgent need to reduce the use of alcohol among women of childbearing age in Russia and to consider the future implications of non-diagnosed FASD in adopted children.[17]

Although it is widely accepted that exposure to high doses of ethanol has long-lasting detrimental effects on brain development, the case for moderate exposure remains controversial,[4 19 20] including studies showing that moderate or low prenatal alcohol exposure is not associated with an increased incidence of social, motor or emotional problems.[21–25] Reasons for discrepancies between these studies could be differences in methodology, demographic characteristics, confounding variables and in accurate determination of

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drinking patterns.[4 21 25 26] The most important shortcoming of these studies is the unacceptable risk assumption. It is not accurate to state that moderate or light drinking does not appear to be associated with adverse mental health consequences: there is no evidence of zero risk. Moreover, the amount of alcohol that reaches the fetus depends not only on the volume of consumed alcohol, but also on genetic or epigenetic factors and on transplacental passage.[27] There is no 100% assurance that there is no risk at all; so, it is mandatory to recommend that women not drink alcohol during pregnancy.[28]

While human epidemiological studies are inconclusive regarding the impact of moderate or low prenatal alcohol exposure, trophoblast cell models, and primate and rodent models of FASD, have convincingly demonstrated significant effects in several brain regions. The collective evidence from the animal studies suggests that moderate or low prenatal alcohol exposure can persistently alter multiple neurotransmitter and neuromodulatory systems throughout the brain, leading to significant neurobehavioral alterations in the offspring.[4 29]

These laboratory findings could be translated to a clinical setting in several ways.[4] First, public education campaigns on the potential effects of moderate or low prenatal alcohol exposure should be widely implemented and training on this important issue should be provided to health professionals involved in the care of pregnant women. Second, when advising women about ethanol consumption during pregnancy, clinicians should consider moderate and low prenatal alcohol exposure as a potential cause of neurobehavioral disorders identified during adulthood. Third, the development of laboratory tests that can objectively assess prenatal alcohol exposure should continue to be pursued actively (maternal hair long enough to reflect hair growths for the entire pregnancy period, and meconium for second and third trimesters). Fourth, the offsprings of mothers who consumed ethanol at any level should be assessed for cognitive alterations at multiple levels and at different stages of development, because deficits could be significantly ameliorated by early behavioural or pharmacological interventions.[10 30–34] Brief interventions that can be delivered by a health professional and that involve motivational interviewing have been demonstrated to significantly reduce alcohol consumption during pregnancy.[33 34]

Organisations such as EUFASD (European Fetal Alcohol Spectrum Disorders) Alliance recommend avoiding ethanol completely (abstinence) throughout pregnancy and also before pregnancy.[19 28] However, institutional guidelines in some countries recommend that women consume no more than a given quantity of ethanol per day.[4 22] However, the effect of ethanol metabolism on the outcome of pregnancy is not fully understood and in humans, the dose–response relationship between prenatal ethanol exposure and fetal effects needs to be better established, taking into consideration not only the dose but also the pattern and timing of exposure.[4 35]

Although brain damage caused by fetal exposure to ethanol cannot be reversed, early action is of extreme importance since appropriate follow-up programmes for affected newborns may prevent the development of secondary disabilities and help lead to the best possible neurodevelopmental outcome.[10] The preventive message must be very clear: no amount of alcohol is safe during pregnancy.[4 19 28 36]

Specialists should make further efforts in identifying the best ways to investigate alcohol consumption in pregnancy in order to implement preventive programmes to avoid alcohol use during pregnancy, and to attain the earliest possible diagnosis and an effective multidisciplinary management with the aim of alcohol-free future pregnancies.[10]

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