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Impact of Fetal Drug Exposures on the Adolescent Brain

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Drug use during pregnancy, which in the United States is estimated at 1 million individuals each year,¹ puts the newborn at increased risk for multiple adverse health outcomes. While the deleterious effects of alcohol, and to a lesser extent nicotine, to the fetus are well recognized, those of illicit drugs are much less understood. Drugs can harm the fetus both via effects to the placenta interfering with nutrient delivery and through direct effects to the fetus. Moreover, the high lipophilicity of drugs ensures that significant concentrations reach the fetus' brain and other organs.² Thus, the consequences of fetal drug exposure on brain development and function, and ultimately on behavior, constitute an important area of research.

The article by Liu et al³ in the current issue is an example of such a study that takes advantage of brain imaging technologies and cognitive assessment in a prospective cohort of 40 adolescents (13-15 years of age) born to mothers who used tobacco (nicotine) or cocaine or both during pregnancy. This study reported distinct brain morphologic effects for these 2 drugs, documenting decreased cortical thickness in the right dorsolateral prefrontal cortex of adolescents exposed to cocaine and decreased volumes in globus pallidus in those exposed to nicotine. It also reported that larger volumes of the thalamus were associated with greater impulsivity both in adolescents exposed to cocaine and in those exposed to nicotine. Since impaired prefrontal cortex is associated with low self-control and impulsivity is a risk factor for substance use disorders, these findings would be consistent with an increased risk for externalizing disorders in those adolescents exposed to cocaine and nicotine during pregnancy. Indeed, smoking during pregnancy may account for up to 25% of externalizing behaviors.⁴

However, from such studies, it is not possible to disentangle the factors that are related to fetal drug exposures from those that pertain to genetic factors that modulate brain development and function, as well as the interactions between specific gene(s) and fetal drug exposures.⁵ For example, there is evidence from brain imaging studies comparing monozygotic and dizygotic twins that the volume of the prefrontal lobe (as well as that of other brain regions)⁶ and cortical thickness⁷ are genetically determined. Similarly, there is increased recognition from preclinical and clinical studies (mostly in adults) that the effects of drugs on the brain are modulated by genetics.⁸⁻¹⁰

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Additionally, genetic factors in the mother are likely to determine during pregnancy who continues to take drugs and who does not, highlighting the importance of controlling for parental characteristics and for relevant environmental exposures (ie, social stress). Drug use during and after pregnancy is likely to influence the interaction of the mother with the infant and the family environment in which the child grows, which in turn can influence brain development. Mothers who abuse drugs during pregnancy are more likely to display impaired parenting skills,¹¹ and in turn poor parental interactions are associated with impaired brain development and function.¹² For example, a recent study showed that cumulative life stress was associated with smaller volumes in the prefrontal cortex,¹³ which in turn mediated the relationship between early childhood stress and impaired working memory.¹⁴

Based on the results of preclinical studies, it is also apparent that doses, drug combinations, and the trimester of exposure influence the outcomes to the fetus.¹⁵ In this respect, drug combinations (particularly those that include alcohol, which is highly teratogenic) are particularly deleterious.

The findings from Liu et al³ highlight the importance of research on fetal drug exposures on brain development and identify the need for developing standards of healthy brain development as a function of sex and age (including pubertal status). Standards for normal brain development and function will require the creation of large brain imaging databases of healthy children that would serve as normative baseline for comparisons, for example, the brain images of children with fetal drug exposures and/or brain diseases. The feasibility of creating such large databases from brain images of children and adolescents is already being realized by several projects including the 1000 Functional Connectomes Project (initiated with brain images from adults and then expanded to children),¹⁶ which integrated images from independent investigators with little standardization as well as projects such as the IMAGEN Study¹⁷ that standardized procedures from the inception. Such databases will also allow researchers to study how genes associated with brain developmental disorders (ie, addiction and schizophrenia) influence brain morphology structure and function. For example, a recent study (n=79) reported that the neuregulin-1 (*NRG-1*) gene, which is a leading candidate gene for schizophrenia, was associated with decreased gray matter volume in the frontal cortex in individuals carrying the risk allele.¹⁸ Replication in larger data sets will allow the assessment of whether *NRG-1*'s modulation of the risk for schizophrenia is mediated by its effects on brain structure.

In parallel, such databases will benefit from detailed phenotypic characterization, ideally along a dimensional continuum, so that particular brain characteristics can be linked to particular outcomes. This is illustrated by a recent study of adolescents (n=1896) in which distinct impulsivity phenotypes were associated with specific neuronal networks, which in turn predicted functional outcomes such as substance use and attention-deficit/hyperactivity disorder symptoms (ie, inattention and impulsivity).¹⁹

Finally, the findings from Liu et al³ demonstrate in humans that both legal and illegal drug exposures during fetal development influence brain structure during adolescence, and they

highlight the urgency of instituting prevention programs against drug use during pregnancy and treatment interventions for pregnant women who abuse drugs.

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