

## The Association Between Maternal Smoking During Pregnancy and Bipolar Disorder in the Offspring: Alternative Interpretations

**M**aternal tobacco smoking during pregnancy has been found to be associated with several adverse pregnancy outcomes in prospective and case-control epidemiological studies. In particular, the association between maternal smoking during pregnancy and small-for-gestational-age births is consistently reported in the literature, shows a clear dose-response effect, and is regarded as causal (1).

A large, although less consistent, body of evidence also supports the association of maternal smoking during pregnancy with cognitive and behavioral problems in the offspring, including a higher frequency of attention, learning, and memory deficits and an increased risk of developing externalizing mental disorders such as attention deficit hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder, and substance use disorders (2).

In this issue, Talati et al. (3) report on a case-control observational study showing, for the first time, that maternal smoking during pregnancy is associated with a nearly twofold greater risk for bipolar disorder in the offspring after adjusting for several potential confounders, including maternal alcohol use and psychiatric history as well as offspring birth weight. The study has several methodological strengths, such as the prospective assessment of maternal smoking, the outcome evaluation carried out many years after the exposure assessment, the use of a population-based birth cohort, and the diagnoses of bipolar disorder made on the basis of direct structured interviews.

Pending replication, how do we interpret this finding? There are two main alternative interpretations. The first is that the association between maternal tobacco smoking during pregnancy and the offspring's risk for bipolar disorder as well as externalizing disorders is explained by the neurotoxic effects of the prenatal exposure to constituents of tobacco smoke (primarily nicotine but also carbon monoxide and possibly others). The second is that the association is spurious, that is, totally explained by environmental and genetic factors related to maternal smoking. A third intermediate possibility is that, although the association is partially confounded, smoking during pregnancy is still one of the environmental factors that may combine, either additively or interactively, with genetic vulnerability, contributing to the risk for bipolar as well as externalizing disorders. Let's briefly review the evidence supporting each of these hypotheses.

The toxic effects of prenatal exposure to nicotine and carbon monoxide are well documented. Both substances readily cross the placenta and reach higher concentrations in the fetal than in the maternal compartment. Nicotine disrupts the function of the placenta and exerts an anorexigenic effect leading to maternal and fetal undernutrition. Carbon monoxide, binding to hemoglobin, forms carboxy-hemoglobin, which results in fetal hypoxia. Furthermore, the direct action of nicotine on the fetal brain has been found in animal studies to produce disturbances in neuronal migration, abnormalities in cell proliferation and differentiation,

and disruptions in the development of cholinergic and catecholaminergic systems (4). So, maternal smoking during pregnancy may increase the risk for bipolar and externalizing disorders by both an indirect and direct impact on neurodevelopment.

However, this is only one part of the story. Pregnant women who smoke may differ from those who do not smoke on several environmental and genetic variables. The decision not to quit smoking during pregnancy may be related to antisocial traits, risk-seeking behavior, or a reduced attention to one's own and the child's well-being. These traits may reflect a familial vulnerability to bipolar disorder, which is transmitted to the offspring. Furthermore, there may be a relationship between maternal smoking during pregnancy and rearing behavior, psychosocial stress, family conflict, and paternal psychiatric history. Smoking during pregnancy is often associated with the use of other substances (such as alcohol) as well as with postnatal smoking. It is also well documented that low education level and economic disadvantage are overrepresented among women who do not quit smoking during pregnancy. In the Talati et al. study, several potential confounders were adjusted for (including maternal psychiatric history), and some variables did not differentiate smoking from nonsmoking mothers (e.g., educational level), but several other variables could not be controlled for (such as maternal personality traits, family history of mental disorders, and smoking after pregnancy). Of note, women smoking in the period 1959–1966, when recruitment for the study took place, were somewhat early adopters, in whom some of the above-mentioned confounding personality traits may have been overrepresented. Furthermore, the study did not explore paternal personal and family psychiatric history.

Indeed, studies controlling for correlates such as life stress, family

conflict, and mother-child attachment reported that maternal smoking during pregnancy was no longer associated with behavioral or emotional problems in the offspring (5). Furthermore, investigations using semiexperimental designs provided evidence that familial factors confound the association between smoking during pregnancy and externalizing disorders. In particular, studies comparing siblings differently exposed to smoking during pregnancy (i.e., born from pregnancies with no or some compared with higher exposure to maternal smoking) reported that these siblings did not differ significantly with respect to conduct and oppositional defiant problems (6). Moreover, in vitro fertilization studies, in which mothers were not genetically related to the offspring but provided the prenatal environment, found no relationship between maternal smoking during pregnancy and ADHD or antisocial behavior (7). These semiexperimental investigations, however, have their own problems: for instance, the sibling-comparison design does not account for factors that may induce women to change their smoking behavior over time.

Even if the association between maternal smoking during pregnancy and risk for bipolar as well as externalizing disorders in the offspring is partially confounded, smoking during pregnancy may still explain some additional variance beyond genetic and other environmental effects. This is suggested by some twin and children-of-twin studies focusing on ADHD and antisocial behavior (2). Moreover, molecular genetic research is providing some evidence of a gene-environment

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interplay involving maternal smoking during pregnancy. It has been reported that variants of genes implicated in the metabolism of tobacco smoke byproducts (maternal CYP1A1, GSTT1, and GSTM1) may moderate the effect of smoking during pregnancy on adverse pregnancy outcomes (8) and that polymorphisms of noradrenaline and dopamine transporter genes in the offspring may interact with maternal smoking during pregnancy in increasing the risk for externalizing behaviors (9, 10).

This latter line of research warrants further development. Although its effect size may not be as great as suggested by observational studies, maternal tobacco smoking during pregnancy may be among the environmental variables contributing to the risk for externalizing disorders and possibly bipolar disorder, adding to or interacting with genetic vulnerability. Of note, it would be one of the most easily modifiable of those risk factors. Testing the magnitude of the effects of various genetic and environmental factors on risk for bipolar and externalizing disorders in offspring clearly requires further studies using genetically sensitive designs.

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