[Archived] Tobacco Consumption During Pregnancy and Its Impact on Child Development: Comments on Fergusson and Fried

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Introduction

Drs. Fergusson and Fried have eloquently summarized the growing body of literature regarding prenatal exposure to cigarettes as a potent risk factor for neuropsychological difficulties and problem behaviour—particularly Conduct Disorder (CD), delinquency and smoking. As they note, the body of existing evidence is consistently supportive, but is not proof, of causality. Along with cumulative evidence, their reviews compellingly lead us to the following points:

a. **There are systematic links between prenatal tobacco exposure and *a specific psychiatric disorder.*** The uniqueness of the association to CD is groundbreaking in the field of behavioural teratology, in contrast with the dearth of systematic behavioural effects of prenatal exposure to illicit drugs.[1,2]

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b. **The identification of a *preventable prenatal* risk factor for CD and youth smoking has profound implications for prevention.** CD and smoking in youth are serious public health problems. While there is increasing evidence that early life events have a long-lasting influence on development,[3] prenatal exposure to smoking is unique as an easily quantified, potentially modifiable risk factor.

c. **The relationship between prenatal exposure to smoking and adverse behavioural outcomes appears complex and non-linear.** Vulnerabilities associated with prenatal exposure to smoking are present during infancy. Modifiable postnatal factors alter risk for exposed infants. There is evidence of sex differences in long-term effects.[4]

d. **Research on the behavioural effects of prenatal exposure to cigarette smoke provides a superb model for studying the interaction of biologic and social processes in developmental psychopathology.**

Research and Conclusions

There are now dozens of studies establishing linkages between prenatal tobacco exposure, postnatal conduct problems and smoking in youth. (For more extensive reviews see reference[5-8]) Fried has also consistently demonstrated an association between exposure and specific neuropsychological difficulties.[9] It is now firmly established that:

a. the association between prenatal exposure to cigarette smoke and adverse behaviours is consistent across diverse populations and developmental periods and is resilient to confounding; and

b. nicotine is a behavioural teratogen.

Thus, Fergusson's conclusion that prenatal exposure to smoking "may" be related to increased risks of adverse behavioural outcomes seems too conservative, based on the state of current knowledge. It seems undeniable that prenatal tobacco exposure is associated with adverse behavioural outcomes. What must now be established is the nature of this association. Since further replication will not add meaningfully to our understanding of this phenomenon, we must boldly move to more explicit testing of causal models and the delineation of pathways.

Fergusson and Fried rightly contend that establishing causality is a daunting task and they highlight critical challenges in this area. However, these challenges should not deter us from designing studies that will enable the field to draw meaningful conclusions from findings

concerning causal mechanisms. The state-of-the-art in this area of research allows us to generate a comprehensive agenda for future research, as follows:

1. **Identification of Underlying Mechanisms**

a. Biologic

Fergusson focuses primarily on the importance of identifying biologic mechanisms, particularly in animal studies. He also underscores the difficulty of translating findings from animal studies to explanations of complex human behaviours. Fortunately, the current state of knowledge allows for integration of basic and observational science, including the embedding of functional imaging and neurochemical techniques within well-executed observational studies of behaviour.[5]

The relatively crude measurement of prenatal tobacco exposure in existing studies has also limited our understanding of biologic mechanisms. The time has now come to conduct prospective studies designed to elucidate teratologic processes in relation to clinical outcomes. Such studies will require a repeated, precise, biologic measurement of exposure to demonstrate dose–response, timing and threshold effects.

b. Developmental

The developmental nature of these processes cannot be overemphasized. Therefore, establishing underlying *developmental* pathways is as vital as the elucidation of purely *biologic* mechanisms. One likely etiologic model: that exposure-related neurobehavioural vulnerabilities increase susceptibility to other risks. Fried's work provides a superb portrayal of the developmental course of such vulnerabilities. However, to date, neurobehavioural and clinical investigations have proceeded separately and clinical studies have focused on discrete disorders rather than on their underlying processes. We now require a more integrative, longitudinal approach that identifies *precursor* vulnerabilities across multiple domains, examines their transformation over time and their independent and interactive contributions to adverse outcomes.[4]

2. Establishing how prenatal tobacco exposure intersects with other risks in pathways to problem behaviours

a. Consideration of alternative explanations

Fried and Fergusson note that obvious confounders have been ruled out at a basic level. Thus, a more sophisticated approach to consideration of alternative explanations is now required. For example, since initial clinical studies were not originally designed to examine the effects of prenatal tobacco exposure, the offspring of smokers were compared to those of non-smokers. These groups differ dramatically at virtually all levels of risk. A more rigorous examination of this question requires a characterization of psychiatric and psychosocial differences between women who quit smoking during pregnancy and those who smoke throughout pregnancy. This examination will lead to the development of testable hypotheses about effects of exposure per se vs. the more ambiguous fact of "having a mother who smokes."

As another example, Fergusson emphasizes genetic factors as a yet unmeasured confound. In fact, genetic factors have been controlled via measurement of parental psychiatric history in virtually all clinical studies. This has not appreciably altered the association. Thus, to date, there is no evidence to support the theory that the smoking–problem behaviour association is spurious to genetic factors. However, because measures of phenotypic expression do not fully capture genotypic variation, statistical control for parental history does not disaggregate the specific role of genetic factors—disaggregation would require genetically informed study designs. Given the current state of knowledge, it may be more fruitful to consider genetic factors as an integral part of a complex, causal process, rather than (primarily) as confounders.

b. Developing and testing integrated models.

We strongly concur with Fried's perspective that the mechanism of effect is likely to involve a complex interaction of factors. Working with this perspective will likely prove more fruitful than an *either/or* approach. Interactions may occur at any point in the developmental pathway, both in utero(eg, genetic susceptibility potentiated by exposure)[8,10] and postnatally (eg, positive home environments reduce risk in early childhood).[4] This approach is complex and requires a carefully designed longitudinal study to establish *for whom, under what circumstances and how* prenatal tobacco exposure is linked to adverse behavioural outcomes.

Implications for the Policy and Services Perspectives

Fergusson wisely cautions against basing policy on premature assumption of causality. On the other hand, Fried convincingly argues that definitive proof of causality is not required to use the accruing body of evidence as a further imperative to intensify prevention efforts.

Given that public health efforts to promote smoking cessation are successful with only a minority of women,[11] these findings further compel us to develop more effective prevention strategies for the pregnant smoker. Generations of children cannot wait. Combined with well-established perinatal consequences, the seriousness of the potential long-term sequelae necessitates a stronger emphasis on harm-reduction.[12] The earlier girls start smoking, the more likely they are to smoke during pregnancy. This creates additional urgency for youth smoking prevention to begin well before adolescence.

The economic burden of smoking has been underestimated because the substantial short- and long-term intergenerational costs have not been included.[13-16] Thus, redoubling efforts to increase resources dedicated to reducing this preventable maternal behaviour is not only a social but also an economic imperative.

In conclusion, Drs Fergusson and Fried have provided us with a comprehensive overview of the state-of-the-art, which serves as a firm foundation for future work. As we move from this foundation to the next stages of scientific discovery, much will be learned, not only about prenatal tobacco exposure and behaviour, but, more broadly, about brain and environment interactions in pathways regarding normal behaviour and psychopathology.

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