Introduction

Dr. Brennan has done a commendable job of highlighting the scientific literature on the linkages between prenatal tobacco exposure and adverse effects on child behaviour. Drs. Fergusson and Fried have gone on to expand this topic to include outcomes on growth and executive functioning. All three excellent reviews point to the growing number of studies that have consistently established links between adverse developmental effects and gestational tobacco exposure. These findings have important public health implications since approximately 12% of pregnant women in the United States smoke during pregnancy, based on birth certificate data, and higher rates are reported through survey data. Smoking rates are even higher among younger women and women from lower socio-economic status populations whose children may be more susceptible than other children to developmental problems.

Research and Context

Drs. Brennan, Fergusson, and Fried

A. Consensus of Findings

1. **Indisputable evidence**: Prenatal tobacco exposure has a causal influence on intrauterine growth retardation resulting in lower birthweight.\(^{1,4-6}\)

2. **Strong and consistent evidence**: Prenatal exposure to tobacco smoke has repeatedly been shown to be related to behavioural problems among offspring, including externalizing, aggression, conduct disorder, hyperactivity, and crime.
3. **Suggested evidence:** There appears to be a catch-up in the growth deficiencies seen at birth, and in several studies, the children have a propensity for increased weight or skinfold thickness. Prenatal exposure to tobacco smoke has been associated with compromised cognitive abilities and executive functioning in verbal intelligence, verbal learning and memory, and auditory processing.

**B. More work is needed**

Drs. Brennan, Fergusson and Fried have detailed several of the methodological problems that continue to plague the study of teratology and that will require more careful attention in future studies, namely:

1. **Covariates of Maternal Smoking**

Drs. Brennan and Fried note that numerous lifestyle variables are related to maternal smoking and need to be measured in order to statistically isolate the effects of prenatal smoking from other effects. More recent studies have very effectively achieved this goal, although no study can control for all environmental/lifestyle variables.

2. **Prospective Study Designs**

Our level of progress in this field now dictates that future studies be prospective in their study design and that the measure of prenatal exposure to tobacco smoke begin early in the pregnancy and be repeated throughout the gestational period. This approach will reduce recall bias and allow for the evaluation of trimester-specific effects in offspring.

3. **Improvement of Exposure Measurement**

Dr Brennan has also suggested that the exclusive use of maternal self-report provides an unreliable measure (as seen across many studies). Exposure measurement could be improved with the addition of certain biological measures. Biological measures of tobacco exposure quantify specific levels of cotinine, a metabolite of nicotine, from body fluids. However, the exclusive use of biological measures is limited by their small window of exposure detection. Using both self-report and biological measures are therefore recommended for future studies.

4. **Understanding of Etiological Mechanisms**

Linkages between prenatal tobacco exposure, development of structural and functional central nervous system (CNS) abnormalities, and the occurrence of cognitive and behavioural dysfunctions are biologically plausible, but the exact mechanism behind these adverse effects remains unclear.

Data from animal and human studies suggest that reduced levels of oxygen play a role in causing the neurobehavioural deficits seen in children who were prenatally exposed to tobacco smoke. Two agents present in tobacco smoke that produce reduced blood oxygen levels are carbon monoxide (CO) and nicotine. Animal studies have demonstrated that fetal hypoxia is associated with deficits in learning and memory tasks, including active avoidance, and non-spatial working memory. In humans, chronic fetal hypoxia is associated with alterations in neurological, behavioural, and emotional functioning.
In addition, nicotine-specific receptors have been identified in the fetal brain. Preclinical studies demonstrate that nicotine is a neuroteratogen that produces CNS abnormalities in rats at exposure levels that correspond to one pack of cigarettes per day in pregnant women. Nicotine infusion into pregnant rats disrupts the normal process of fetal brain development and produces long-term hypoactivity or reduced responsivity in synaptic function. The cholinergic neurotransmitter system may be affected by prenatal nicotine exposure, affecting learning and memory deficits and performance in maze learning tasks, although there is evidence that multiple neurotransmitter pathways are involved. These CNS effects may explain some of the linkages found between prenatal exposure to tobacco smoke and neuropsychological outcomes.

5. Control for Potential Genetic Confounding

Drs Fried and Fergusson have discussed the important genetic component that is often overlooked in teratology studies: Are the mothers who smoke during pregnancy more likely to have and pass on the particular genotypes that are associated with externalizing behaviours or impulsivity? Measures of aggression, hostility, impulsivity, etc. should be conducted with the parents and statistically controlled for in analyses when examining the effects of prenatal exposure to tobacco smoke in these outcomes of their offspring.

C. Additional Questions for Future Study

1. Is there a critical period during which the central nervous system is especially vulnerable to the effects of prenatal tobacco exposure?

Studies of fetal human brain tissue have identified the second and third trimesters as the periods in which the CNS of the fetus is particularly sensitive to the teratogenic effects of nicotine. It is during this period that the density of nicotinic receptor binding sites begins to increase appreciably. Previous behavioural research has indicated that exposure during the latter half of pregnancy may be particularly deleterious as effects on verbal learning decrements and increased perseverative responses have been noted. In other reports, third-trimester exposure was the best predictor of behavioural effects. Yet other researchers have noted that when mothers stop smoking during pregnancy, their offspring perform significantly better on measures of cognitive functioning compared to children of mothers who smoked throughout pregnancy. However, these results must be viewed with a degree of caution. Timing of exposure is confounded with duration and dose; women who quit smoking earlier in pregnancy typically smoke less than those who smoke across all three trimesters.

2. What are the implications of the effects of environmental tobacco smoke exposure?

Another related area of study that has received less attention is that of passive tobacco exposure in both the postnatal and prenatal periods. Women who do not smoke during pregnancy may expose the fetus through passive exposure to smoke from other household smokers. Furthermore, women who quit smoking during pregnancy are particularly vulnerable to smoking relapse after delivery, so their children are at higher risk of being exposed to environmental tobacco smoke (ETS). ETS in both the pre- and postnatal environments has been reported to negatively affect growth, cognitive, behavioural, and neuropsychological outcomes in offspring. Postnatal tobacco smoke exposure has also been cited as a factor in the increased risk of Sudden Infant Death Syndrome, asthma, acute and chronic respiratory problems, and otitis media.
3. **Do offspring who are exposed to tobacco smoke in the womb have a predisposition to become smokers?**

Recent studies have reported that there is an increased predisposition to smoke among offspring who were prenatally exposed to maternal smoking.\(^ {67-69}\) This linkage is biologically plausible, as seen in animal studies.\(^ {70-72}\) However, more research is required in this area to carefully control for environmental and genetic factors and consider factors that may mediate this linkage, such as certain behavioural outcomes.\(^ {68}\)

**Implications for Policy and Services**

Establishing causal links requires a replication of findings across a large number and variety of study populations as well as biological plausibility for linkages. As indicated in three excellent reviews by Brennan, Fergusson, and Fried, prenatal exposure to tobacco smoke has consistently been linked to adverse effects on neonatal growth, long-term growth effects, behaviour, and cognitive abilities.

As an epidemiologist, I am reminded of the health-promoting practices of John Snow. Snow removed the handle off the Broad Street water pump during the 1853 outbreak of cholera in London, England following his consistent observations that people who drank water from the Broad Street pump were more likely to die from cholera.\(^ {73}\) Snow's actions prevented many deaths, even though he knew nothing about the microbiology of cholera. One of the benefits of epidemiology is that it suggests health-promoting practices before biological mechanisms are completely understood. Linkages between prenatal exposure to tobacco smoke and the occurrence of behavioural and cognitive dysfunctions have been consistently observed, and the etiology of these associations is gradually becoming better understood.

Pregnancy is often considered an opportunistic window for behavioural change because women are more likely to stop smoking during pregnancy, both spontaneously\(^ {74,75}\) and with assistance\(^ {76,77}\) than at other times in their lives. However, since many women relapse after delivery,\(^ {52-54}\) smoking cessation programs need to focus on lifetime cessation rather than simply prenatal cessation. As public health professionals, we are at an important juncture in our scientific knowledge that lends itself to a more comprehensive primary prevention approach. It therefore behoves us to work to prevent our youth from starting to smoke and to intervene with lifelong cessation programs that target sexually active women who smoke.

**References**


32. Giustino A, Cagiano R, Carratù MR, Cassano T, Tattoli M, Cuomo V. Prenatal exposure to low concentrations of carbon monoxide alters


