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Prenatal Cigarette Smoke Exposure: Effects on Offspring

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Introduction

Over 20% of North American and Canadian adults smoke despite the fact that cigarette smoking is the leading cause of preventable morbidity and mortality.[1,2] Tobacco is also the most commonly used substance during pregnancy;[3] 13.8% of pregnant American women smoke[4] and 10.5% of pregnant Canadian women smoke[5] affecting more than 600,000 live births per year.

Subject and Research Context

The scientific literature is replete with findings of adverse prenatal cigarette smoke exposure (PCSE) effects on offspring. More recent studies have improved on earlier methodologies with prospective designs, biological measures and statistical control of confounders. Many of these studies also use more sophisticated measures including objective *neurobehavioural test batteries*, *neuroimaging techniques* and assessment of *genotypic variability*. This brief synopsis will focus on studies published since the previous report on this topic by Peter Fried.[6]

Recent Research Results

The evidence is clear about PCSE's causal effects on neonatal morbidity and mortality,[7] and its effects on neurobehaviour is a recent focus in the infancy literature. PCSE is associated with infant irritability, inattention, decreased response to inanimate auditory stimuli,[8] *increased hypertonicity*[9] and more problematic temperament.[10] Key et al.[11] found that PCSE infants discriminated fewer syllables and processed them more slowly than non-exposed infants. Similarly, Golub and colleagues[12] demonstrated that exposed nonhuman primates showed less novelty preference in visual recognition.

Studies on the effects during childhood continue to show that PCSE is a consistent predictor of higher rates of problems such as language delay in preschoolers,[13] externalizing and internalizing behavioural problems such as acting out or withdrawal in 2-year-old children,[14] child aggression in 17- to 42-month olds,[15] and externalizing in early childhood that persists to age 18.[16] Studies have also considered the effects of both prenatal and postnatal tobacco smoke exposure and have demonstrated an independent effect of PCSE on childhood behaviour problems at ages 6[17] and 10.[18,19] In a large multinational study, Brion et al.[2] reported a direct relation between PCSE and offspring conduct and externalizing problems. In a clinical sample of children with ADHD, hyperactive-impulsive symptoms and conduct disorder symptoms were significantly higher among those with PCSE.[21] Others have found a relation between PCSE and conduct disorder symptoms.[22,23] Murray and colleagues[23] found that this relation between PCSE and conduct disorder symptoms in childhood extended to criminal behaviours when the offspring were ages 30-34. PCSE also has long-term effects on physical health in offspring. Johansson et al.[24] found timing effects in offspring wheezing, sleeping difficulties, excessive crying, and use of bronchodilating drugs depending on whether exposure was prenatal only, postnatal only, or both. Gilman et al.[25] examined over 52,000 children from birth to age 7 and found that low birth weight and a higher odds for being overweight were associated with PCSE. In two meta-analyses,[26,27] PCSE was significantly related to offspring obesity and overweight, respectively. Rooney et al.[28] also found that PCSE was a significant predictor of obesity in a birth cohort during adolescence and adulthood.

Recent studies on the effects of PCSE on risk for smoking in offspring have replicated and extended earlier reports. Menezes et al.[29] found this relation in early adolescence. Agrawal and colleagues[30] demonstrated that PCSE was associated with earlier age of initiation as well as earlier regular smoking. O'Callaghan and colleagues[31] reported this relation with nicotine dependence in young adulthood. Lotfipour and colleagues[32] reported an interactive effect between in utero tobacco smoke exposure *polymorphism* in the *nicotinic acetylcholine* receptor that influences

smoking and other drug use. Underscoring these findings in an animal model, Slotkin et al.[33] noted that both prenatal and adolescent nicotine exposures resulted in permanent changes in synaptic function, and prenatal exposure sensitized females to the subsequent effects of nicotine.

With the development of faster genetic mapping techniques, more studies have incorporated genetics into their designs, documenting interaction effects of PCSE and genetic liability on outcomes. One such design found a dampened response to novelty among PCSE infants with genetic variability in the *DRD2* gene.[34] In another study,[35] 15-year-old males with PCSE who were *homozygous* for the DAT1 dopamine transporter gene had higher rates of hyperactivity and impulsivity than all other groups.

Similarly, Neuman[36] found that the odds of a *DSM-IV* Attention Deficit Hyperactivity Disorder (ADHD) diagnosis were 2.9 times greater in twins with the *DAT1 allele*, 2.6 times greater in those with the *DRD4* seven-repeat allele, and 9.0 for offspring with PCSE and both alleles. Wakschlag and colleagues[37] tested the effects of a polymorphism of the enzyme *monomine oxidase* (MAOA) and PCSE on antisocial behaviour in adolescents demonstrating that *MAOA genotype*, PCSE and gender interact to predict antisocial behaviour in exposed male offspring.

Brain imaging studies have also advanced our knowledge about the mechanisms that may drive PCSE effects. Rivkin[38] examined the brain volume in a*magnetic resonance imaging (MRI)* study of 10- to 14-year-olds. PCSE was associated with significant reduction in cortical gray matter and total *parenchymal* volumes and head circumference. In another MRI study, Toro et al.[39] found that orbitofrontal, middle frontal, and *parahippocampal* cortices were thinner in the PCSE- exposed adolescents. Jacobsen et al.[40] used MRI and *diffusion tensor imaging (DTI)* to examine effects of prenatal and adolescent tobacco exposure on structure of brain white matter and found that both white matter microstructure and auditory processing were affected indicating that nicotine-induced disruption of the auditory *corticofugal fibers* may lead to reduced efficiency in auditory processing. In another study by Jacobsen and colleagues,[41] PCSE and exposure during adolescence was found to exert gender-specific deleterious effects on auditory and visual attention *fMRI (functional magnetic resonance imaging)*.

Research Gaps

Despite the mounting body of evidence linking PCSE to problems for offspring, several recent studies have not found significant associations.[42,43,44,45,46] These results suggest that it is important

to consider factors that may account for the explained variance in outcomes, many of which are also related to smoking during pregnancy, such as lower education and income. Several review articles have synthesized PCSE effects,[47,48,49] with some reviews including non-human data.[50,51,52] One recent review[53] of the long-term consequences of fetal and neonatal nicotine exposure highlights concerns about the safety and utility of nicotine replacement therapy during pregnancy. Suggestions from reviews to address current gaps in the literature include: considering multiple factors in explaining the nature of attention hyperactivity disorder and behavioural problems; attaining an unbiased estimate of the magnitude of the association between exposure and outcome, and more comprehensive study designs that involve the gene-environment interplay.

Conclusions

The large majority of recent studies have built upon the evidence of the last five decades that smoking during pregnancy is deleterious for multiple offspring outcomes and that these effects can be detected from infancy through adulthood. However, based on some of the studies with negative findings, it is apparent that there is a need for adequate control of potential confounds that may also contribute to these outcomes. Establishing causal links requires replication of findings across large numbers of studies with varying study populations. Part of the difficulty in concluding causal effects is due to the inability to separate prenatal exposure effects from other confounding environmental and genetic factors. New research examining genetic liability suggests that PCSE may interact with genes to produce effects. Animal models offer added support for linkage by supporting biological plausibility for such relations. Imaging techniques provide visible effects of exposure on brain structure and function. Although the mechanisms of PCSE's effects on the developing brain are not completely understood, newer research informs us that the mechanisms are multifactorial, involving biological effects, genetic susceptibility, and environmental factors.

Implications for Parents, Services, Policy

Since 1957 a plethora of studies have implicated PCSE with multiple adverse outcomes in offspring from birth through adulthood.[54] It is encouraging that rates of smoking during pregnancy have decreased in the past decade, but the prevalence is still too high, especially for specific groups that are already at higher risk for fetal problems such as teenagers and women of low-economic status. Public health efforts that have proved to be efficacious in reducing smoking should continue to receive support. With evidence of nicotine vulnerability among those prenatally

exposed, stopping exposure in the first place, will not only prevent neurotoxicological effects in the offspring, but will prevent continuing smoking exposure in succeeding generations. There is now notable evidence that preventing PCSE may help prevent smoking uptake during adolescence in offspring. Based on what we do know, it is clear that women who are pregnant or who may become pregnant should abstain from smoking and nicotine exposure.

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