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Developmental consequences of prenatal tobacco exposure

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Abstract

Purpose of review—This paper reviews results from published, in press, and conference proceedings from 2007 and 2008 that link in-utero tobacco exposure to neurodevelopmental outcomes in exposed offspring.

Recent findings—Prenatal tobacco exposure (PTE) affected speech processing, levels of irritability and hypertonicity, attention levels, ability to self-regulate, need to be handled, and response to novelty preference in infants. In early childhood, PTE effects were mostly behavioral outcomes including activity and inattention and externalizing behaviors, including conduct disorder and antisocial behavior. In adolescents, PTE predicted increased attention deficit hyperactivity disorder, modulation of the cerebral cortex and white matter structure, and nicotine addiction. Several studies found moderating effects with PTE and genetic susceptibilities including dopamine transporter, serotonergic synaptic function, and monomine oxidase pathways. Other studies suggested that environmental and genetic factors might be more important than the direct teratological effects of PTE.

Summary—The majority of studies reviewed were prospective and tobacco exposure was quantified biologically. Most demonstrated a direct association between PTE and neurodevelopmental outcomes. More work is needed to examine multifactorial influences. Effects of PTE on the offspring appear to be moderated by genetic variability, neurobehavioral disinhibition, and sex.

Keywords

development; pregnancy; tobacco

Introduction

Tobacco is the most commonly used substance during pregnancy [1]: up to 25% of pregnant women smoke [2,3].

Nicotine crosses the placenta and is concentrated in the fetal tissue. The direct effects of nicotine predict deficits in growth and neural development, which have long-term effects on brain function, cognition, and behavior. Indirectly, nicotine affects size through placental pathology [4].

Recent studies have improved on earlier methodologies with prospective designs, biological measures, and statistical control of confounders. Current research also uses more sophisticated assessments including objective neurobehavioral batteries, neuroimaging techniques, and measurement of genotypic variability.

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Neonatal and infant outcomes

Most recent research on infants has focused on behavior. Using the Brazelton Neonatal Behavioral Assessment Scale, one study [5••] compared 25 infants of women who smoked at least five cigarettes per day to 25 infants of nonsmokers. Urine cotinine levels significantly correlated with infant irritability, attention, and decreased response to inanimate auditory stimuli. Paternal smoking, in the absence of maternal use, was also significantly correlated with infant cotinine level and irritability.

Another study [6] examined 962 mother/infant pairs from the Providence Cohort of the National Collaborative Perinatal Project using the Graham-Rosenblith Behavioral Examination of the Neonate. Prenatal tobacco exposure (PTE) was associated with increased irritability and hypertonicity controlling for maternal socioeconomic status (SES), age, race, and infant birthweight. This study represented the largest investigation of the effects of maternal smoking on examiner-assessed neonatal behavior.

In a pilot study, Stroud *et al*. [7] compared 28 infants with PTE to 28 infants of nonsmokers aged 10–27 days. Infants with PTE had a greater need for handling and scored lower on self-regulation. In contrast to prior studies, there were no effects of PTE on abstinence withdrawal symptoms or muscle tone. The authors concluded that effects at this age included poorer infant self-regulation and an increased need for external intervention.

Infant temperament at 9 months was studied in a cohort of over 18 000 infants [8•]. Infants of heavy smokers scored least well on the Carey Infant Temperament Scale, whereas women who quit smoking had infants with higher scores on the easy temperament scale. These findings remained robust after controlling for sociodemographic factors that correlated with maternal pregnancy smoking status.

Six-month-old infants with PTE had less focused attention, lowered reactivity to basic sensory stimulation, and more distractibility compared to nonexposed infants (Wiebe, unpublished data), and the author concluded that PTE leads to deficits in information processing and self-regulation. An additional study by the same author and colleagues evaluated the genetic aspects of PTE-associated neurobehavioral deficits [9•]. This study examined early infant neurobehavior of 119 mothers and their infants. PTE status was based on self-report and maternal and meconium cotinine. The dopamine receptor D2 genotypes of the infants were identified. Nonexposed infants with the A1+ genotype had a heightened response to novelty. Among PTE infants with this variant, however, the response to novelty was dampened, which suggests that genetic variability and PTE interact to affect infant development.

In a study of infant cognition, speech-processing ability was assessed between eight PTE and eight non-PTE infants [10•]. Using event-related potentials, exposed infants discriminated fewer syllables and processed them more slowly than nonexposed infants. Thus, PTE may lead to changes in brain physiology that affect basic perceptual skills.

A study from the animal literature reported on gestational exposure and visual recognition memory. Golub *et al*. [11•] examined rhesus monkeys that were exposed to environmental tobacco smoke (ETS) from gestation day 50 to delivery. In parallel with the human literature, the exposed group showed less novelty preference in the visual recognition task. However, unlike the human literature, no effects were found on the auditory function test. The authors concluded that ETS exposure during pregnancy had adverse effects on cognitive function in nonhuman primates.

Childhood outcomes

Studies of PTE effects in childhood dealt primarily with behavior as the outcome. In a study of 2-year-old children in New Zealand [12•], PTE was assessed retrospectively at the 6-week postpartum visit. The Child Behavior Checklist (CBCL) was completed by the mothers when their children were 24 months old. Tobacco-exposed children had higher rates of internalizing, externalizing, and total problem scores after controlling for prenatal alcohol exposure, sociodemographic factors, maternal health, and parenting practices.

A prospective study examined the role of PTE on child behavioral outcomes in a cohort of teenaged mothers and their offspring. In a report on 357 6-year-olds, PTE predicted increased activity, inattention, and behavior problems on the CBCL after controlling for the correlates of maternal smoking [13•]. In a later report [14•] on the same children at age 10, PTE predicted more activity, impulsivity, delinquent, and aggressive behaviors, and more deficits of selective attention and response on the Stroop test. These effects were found at PTE levels as low as 10 cigarettes per day after controlling for confounders.

A study of maternal smoking during pregnancy and maternal exposure to environmental tobacco smoking (ETS) during pregnancy [15••] found that 7–15-year-old offspring of mothers with only second-hand exposure during pregnancy also had more conduct disorder symptoms after effects of income, parental antisocial tendencies, prematurity, birthweight and parenting practices were controlled. This was the first study to demonstrate the effects of ETS on externalizing behavior in exposed offspring.

Langley *et al*. [16•] examined the roles of PTE, birthweight, and social class among children diagnosed with attention deficit hyperactivity disorder (ADHD). In this clinical population, hyperactive-impulsive symptoms and conduct disorder symptoms were significantly higher among those with PTE, compared to children with ADHD and no PTE.

Multifactorial studies

Several studies have identified factors that interact with the effects of PTE. Huijbregts *et al*. [17•] examined PTE, parental antisocial behavior, and childhood physical aggression in children aged 17–42 months. There was a significant direct effect of PTE on child aggression. The interaction of PTE and the mother's history of antisocial behavior also predicted increased childhood aggression, as did an interaction between PTE and lower family income.

Other outcomes

Lewis *et al*. [18] compared children with and without PTE on receptive, expressive, and total language scores. PTE was significantly related to lower receptive language scores but not expressive language scores.

In a study of somatic outcomes [19], the effects of PTE were explored among 8000 children who were exposed to tobacco prenatally only, postnatally only, and at both times. At 3 years, those exposed both prenatally and postnatally had more wheezing, used more bronchodilating drugs, and had more excessive crying. Those with only prenatal exposure used more bronchodilating drugs and suffered from more sleep problems. Children with only postnatal exposure had more rhinitis, used more cough medicines, and suffered from poorer sleep.

Contrary findings

In contrast to the studies above, Ro*za et al*. [20•] found no increased risk of behavioral problems in a Dutch sample of 18-month-olds who were prenatally exposed to maternal and paternal smoking after controlling for the effects of SES and parental psychopathology.

In a longitudinal study [21•] of 11 192 offspring between the ages of 4–10 years, offspring with PTE were compared to siblings with no PTE. PTE did not predict delinquency or oppositional/defiant behaviors. There was a significant association between PTE, attention, and hyperactivity problems, however. These authors concluded that environmental factors accounted for the association between PTE and externalizing behavior problems.

Gilman *et al*. [22•] examined over 52 000 children from birth to age 7 years. Only low birth weight and higher odds for being overweight at age 7 were associated with PTE. Intelligence, academic achievement, conduct problems, and asthma were not associated with PTE. The authors argued that the effects of smoking during pregnancy may not be distinguishable from a broader range of familial factors associated with maternal smoking.

Adolescent outcomes

With the development of faster genetic mapping techniques, more studies have incorporated genetics into their designs.

Genetics

Becker *et al*. [23••] genotyped 305 15-year-olds, focusing on the dopamine transporter *DAT1* gene and assessed inattention, hyperactivity, impulsivity, oppositional defiant, and conduct disorders using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS). Males with PTE who were homozygous for *DAT1* 10r had higher rates of hyperactivity and impulsivity than all other groups. This study showed the importance of multiple factors in explaining the nature of attention and hyperactivity disorders.

Neuman [24•] examined the *DAT1* and *DRD4* polymorphisms among 1540 twins age 7–19 years. The odds of a DSM-IV ADHD diagnosis were 2.9 times greater in twins with the *DAT1* allele and 2.6 times greater in those with the *DRD4* seven-repeat allele. The odds ratio for offspring with PTE and both alleles was 9.0. The authors suggested that PTE was associated with specific subtypes of ADHD in genetically susceptible children.

Wakschlag *et al.* [25] tested the effects of a polymorphism of the enzyme monoamine oxidase (*MAOA*) and PTE on antisocial behavior in 176 adolescents. PTE males with low activity MAOA 5′ had an increased risk of conduct disorder symptoms as measured by a face-processing task. There was no evidence of a gene–environment correlation among female adolescents. This study showed that *MAOA* genotype, PTE and sex interact to predict antisocial behavior.

Imaging

Rivkin *et al*. [26•] examined the brain volume on MRI of 10–14-year-olds with PTE. PTE was associated with significant reduction in cortical gray matter and total parenchymal volumes and head circumference after adjustment for demographics and the other prenatal substance exposures.

The thickness of the cerebral cortex was measured using MRI in 144 adolescents with PTE and 159 nonexposed adolescents [27•]. Orbitofrontal, middle frontal, and parahippocampal cortices were thinner in the exposed adolescents and more pronounced in females. There was no effect of PTE on IQ. Exposed adolescents scored lower on the Positive Youth Development (PYD), and their scores correlated with their orbitofrontal thickness.

Jacobsen *et al*. [28•] used MRI and diffusion tensor imaging (DTI) to examine effects of prenatal and adolescent tobacco exposure on structure of brain white matter. The sample included 67 adolescent smokers and nonsmokers with and without PTE. PTE and adolescent

tobacco exposure were associated with increased fractional anisotropy in anterior cortical white matter. In another study of auditory and visual attention, females with PTE or adolescent smoking had reductions in auditory and visual attention performance accuracy: these deficits were largest in female smokers with PTE [29•]. Among males, combined exposure predicted deficits in auditory attention. PTE and exposure to nicotine during adolescence had sex-specific effects on auditory and visual attention.

Comparable differences by sex were seen in rats. Deficits associated with PTE in cerebrocortical choline acetyltransferase activity and hemicholinium-3 binding to presynaptic choline transporter were greater in males than females [30••]. Environmental tobacco exposure of the rats in adolescence also affected expression of 5HT in males. When animals were exposed at both periods, the effects were also found in females.

Reviews

Four review articles on PTE were written over 2 years. Shea and Steiner [31] reviewed the animal and human data that linked PTE to neurodevelopmental outcomes. Pickett and Wakschlag [32] reviewed the perinatal consequences of PTE and cognition and behavioral problems linked to PTE. They discussed the inconsistencies in the literature and stressed that PTE should be viewed as a risk for vulnerability along with multiple factors that influence neurobehavioral outcomes. The Button *et al*. [33] paper focused on the effects of PTE on problem behaviors; attention, hyperactivity, and conduct problems. Slotkin [34••] summarized literature from animal and human studies of neurobehavioral and brain development that could alter the reward systems that reinforce subsequent susceptibility to nicotine addiction in later life.

Conclusion

Most studies demonstrate that PTE predicts adverse neurodevelopmental outcomes, although a few reports do not support this conclusion. This may result from differing methodologies, small sample sizes, and differing measurement of PTE, outcomes, and confounders. Imaging techniques continue to demonstrate an effect of exposure on brain function and structure. The mechanisms of PTE's effects on the developing brain are not yet known. It is clear, however, that the mechanism will be multifactorial, involving biological effects, genetic susceptibility, and environmental factors. Animal studies provide biological plausibility to relations found in human populations and corroborate the importance of environmental factors.

Acknowledgments

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 190–191).

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