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

Marie D. Cornelius, PhD

University of Pittsburgh, School of Medicine, USA

March 2003

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

©2003-2025 ABILIO | TOBACCO AND PREGNANCY

rates are reported through survey data.[1] 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.[1-3]

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.[7-15]
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.[16-18] Prenatal exposure to tobacco smoke has been associated with compromised cognitive abilities and executive functioning in verbal intelligence,[19] verbal learning and memory,[20] and auditory processing.[21]

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.[22] However, the exclusive use of biological measures is limited by their small window of exposure detection.[23] 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[7-21] 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.[24-27] Animal studies have demonstrated that fetal hypoxia is associated with deficits in learning and memory tasks, including active avoidance,[28-30] and non-spatial working memory.[31] In humans, chronic fetal hypoxia is associated with alterations in neurological, behavioural, and emotional functioning.[32,33]

In addition, nicotine-specific receptors have been identified in the fetal brain.[34,35] Preclinical studies demonstrate that nicotine is a neuroteratogen[26] that produces CNS abnormalities in rats at exposure levels that correspond to one pack of cigarettes per day in pregnant women.[36] Nicotine infusion into pregnant rats disrupts the normal process of fetal brain development[37,38] and produces long-term hypoactivity or reduced responsivity in synaptic function. The cholinergic neurotransmitter system may be affected by prenatal nicotine exposure,[39] affecting learning and memory deficits[40-44] and performance in maze learning tasks,[45,46] although there is evidence that

multiple neurotransmitter pathways are involved.[47] These CNS effects may explain some of the linkages found between prenatal exposure to tobacco smoke and neurospsychological outcomes.[19-21]

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.[34,47] 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.[20] In other reports,[7,48] 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.[49] 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.[50,51] 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,[52-54] 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.[55-61] 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. [62-66]

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

1. United States. Public Health Service. Office of the Surgeon General. *Women and Smoking: A Report of the Surgeon General*. Rockville, MD: US Dept of Health and Human Services, Public Health Service, Office of the Surgeon General; 2001.
2. Cornelius MD, Day NL, Richardson GA, Taylor PM. Epidemiology of Substance Abuse During Pregnancy. In: Ott PJ, Tarter RE, Ammerman RT, eds. *Sourcebook on Substance Abuse: Etiology, Epidemiology, Assessment and Treatment* Boston, MA: Allyn & Bacon; 1999:1-13.
3. Cornelius MD. Adolescent pregnancy and the complications of prenatal substance use. *Physical and Occupational Therapy in Pediatrics* 1996;16(1-2):111-123.
4. Simpson WJ. A preliminary report of cigarette smoking and the incidence of prematurity. *American Journal of Obstetrics and Gynecology* 1957;73(4):808-815.
5. Floyd RL, Rimer BK, Giovino GA, Mullen PD, Sullivan SE. A review of smoking in pregnancy: effects on pregnancy outcomes and cessation efforts. *Annual Review of Public Health* 1993;14:379-411.
6. Cornelius MD, Taylor PM, Geva D, Day NL. Prenatal tobacco and marijuana
7. use among adolescents: effects on offspring gestational age, growth and morphology. *Pediatrics* 1995;95(5):738-743.
8. Day NL, Richardson GA, Goldschmidt L, Cornelius MD.Effects of prenatal tobacco exposure on preschooler's behavior. *Journal of Developmental and Behavioral Pediatrics* 2000;21(3):180-188.
9. Fergusson DM, Horwood LJ, Lynskey MT. Maternal smoking before and after pregnancy: effects on behavioral outcomes in middle childhood. *Pediatrics* 1993;92(6):815-822.
10. Niaura R, Bock B, Lloyd EE, Brown R, Lipsitt LP, Buka SL. Maternal transmission of nicotine dependence: psychiatric, neurocognitive and prenatal factors. *American Journal on Addictions* 2001;10(1):16-29.
11. Weitzman M, Gortmaker S, Sobol A. Maternal smoking and behavior problems of children. *Pediatrics* 1992;90(3):342-349.
12. Milberger S, Biederman J, Faraone SV, Chen L, Jones J. Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children? *American Journal of Psychiatry* 1996;153(9):1138-1142.
13. Wakschlag LS, Lahey BB, Loeber R, Green SM, Gordon RA, Leventhal BL. Maternal smoking during pregnancy and the risk of conduct disorder in boys. *Archives of General Psychiatry* 1997;54(7):670-676.
14. Weissman MM, Warner V, Wickramaratne PJ, Kandel DB. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry* 1999;38(7):892-899.
15. Brennan PA, Grekin ER, Mednick SA. Maternal smoking during pregnancy and adult male criminal outcomes. *Archives of General Psychiatry* 1999;56(3):215-219.
16. Räsänen P, Hakko H, Isohanni M, Hodgins S, Järvelin MR, Tiihonen J. Maternal smoking during pregnancy and risk of criminal behavior among adult male offspring in the Northern Finland 1966 birth cohort. *American Journal of Psychiatry*

1999;156(6):857-862.

17. Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology* 1999;21(5):513-525.
18. Vik T, Jacobsen G, Vatten L, Bakketeig LS. Pre- and post-natal growth in children of women who smoked in pregnancy. *Early Human Development* 1996;45(3):245-255.
19. Cornelius MD, Goldschmidt L, Day NL, Larkby C. Alcohol, tobacco and marijuana use among pregnant teenagers: 6-year follow-up of offspring growth effects. *Neurotoxicology and Teratology* 2002;24(6):703-710.
20. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12- year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicology and Teratology* 1998;20(3):293-306.
21. Cornelius MD, Ryan CM, Day NL, Goldschmidt L, Willford JA. Prenatal tobacco effects on neuropsychological outcomes among preadolescents. *Journal of Developmental and Behavioral Pediatrics* 2001;22(4):217-225.
22. Fried PA, Watkinson B, Siegel LS. Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology* 1997;19(3):171-183.
23. Benowitz NL, ed. *Nicotine Safety and Toxicity.* New York, NY: Oxford University Press; 1998.
24. Knight GJ, Palomaki GE, Lea DH, Haddow JE. Exposure to environmental tobacco smoke measured by cotinine 125I-radioimmunoassay. *Clinical Chemistry* 1989;35(6):1036-1039.
25. Olds D. Tobacco exposure and impaired development: a review of the evidence. *Mental Retardation and Developmental Disabilities Research Reviews* 1997;3(3):257-269.
26. Lambers DS, Clark KE. The maternal and fetal physiologic effects of nicotine. *Seminars in Perinatology* 1996;20(2):115-126.
27. Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? *Journal of Pharmacology and Experimental Therapeutics* 1998;285(3):931-945.
28. Salafia C, Shiverick K. Cigarette smoking and pregnancy, II: vascular effects. *Placenta* 1999;20(4):273-279.
29. De Salvia MA, Cagiano R, Carratù MR, Di Giovanni V, Trabace L, Cuomo V. Irreversible impairment of active avoidance behavior in rats prenatally exposed to mild concentrations of carbon monoxide. *Psychopharmacology* 1995;122(1):66-71.
30. Di Giovanni V, Cagiano R, De Salvia MA, Giustino A, Lacomba C, Renna G, Cuomo V. Neurobehavioral changes produced in rats by prenatal exposure to carbon monoxide. *Brain Research* 1993;616(1-2):126-131.
31. Mactutus CF, Fechter LD. Moderate prenatal carbon monoxide exposure produces persistent, and apparently permanent, memory deficits in rats. *Teratology* 1985;31(1):1-12.
32. Giustino A, Cagiano R, Carratù MR, Cassano T, Tattoli M, Cuomo V. Prenatal exposure to low concentrations of carbon monoxide alters habituation and non-spatial working memory in rat offspring. *Brain Research* 1999;844(1-2):201-205.
33. Seidman LJ, Buka SL, Goldstein JM, Horton NJ, Rieder RO, Tsuang MT. The relationship of prenatal and perinatal complications to cognitive functioning at age 7 in the New England Cohorts of the National Collaborative Perinatal Project. *Schizophrenia Bulletin* 2000;26(2):309-321.
34. Buka SL, Tsuang MT, Lipsitt LP. Pregnancy/delivery complications and psychiatric diagnosis: a prospective study. *Archives of General Psychiatry* 1993;50(2):151-156.
35. Cairns NJ, Wonnacott S. [3H](-)nicotine binding sites in fetal human brain. *Brain Research* 1988;475(1):1-7.

36. Slotkin TA, Orband-Miller L, Queen KL. Development of [3H]nicotine binding sites in brain regions of rats exposed to nicotine prenatally via maternal injections or infusions. *Journal of Pharmacology and Experimental Therapeutics* 1987;242(1):232-237.

37. Murrin LC, Ferrer JR, Zeng WY, Haley NJ. Nicotine administration to rats: methodological considerations. *Life Sciences* 1987;40(17):1699-1708.

38. Roy TS, Andrews JE, Seidler FJ, Slotkin TA. Nicotine evokes cell death in embryonic rat brain during neurulation. *Journal of Pharmacology and Experimental Therapeutics* 1998;287(3):1136-1144.

39. Navarro HA, Seidler FJ, Schwartz RD, Baker FE, Dobbins SS, Slotkin TA. Prenatal exposure to nicotine impairs nervous system development at a dose which does not affect viability or growth. *Brain Research Bulletin* 1989;23(3):187-192.

40. Zahalka EA, Seidler FJ, Lappi SE, McCook EC, Yanai J, Slotkin TA. Deficits in development of central cholinergic pathways caused by fetal nicotine exposure: differential effects on choline acetyltransferase activity and [3H]hemicholinium-3 binding. *Neurotoxicology and Teratology* 1992;14(6):375-382.

41. Muir JL. Acetylcholine, aging, and Alzheimer's disease. *Pharmacology, Biochemistry, and Behavior*1997;56(4):687-696.

42. Steckler T, Sahgal A. The role of serotonergic-cholinergic interactions in the mediation of cognitive behaviour. *Behavioural Brain Research* 1995;67(2):165-199.

43. Levin ED, Simon BB. Nicotinic acetylcholine involvement in cognitive function in animals. *Psychopharmacology* 1998;138(3-4):217-230.

44. Aigner TG. Pharmacology of memory: cholinergic-glutaminergic interactions. *Current Opinion in Neurobiology* 1995;5(2):155-160.

45. Levin ED, Wilkerson A, Jones JP, Christopher NC, Briggs SJ. Prenatal nicotine effects on memory in rats: pharmacological and behavioral challenges. *Developmental Brain Research* 1996;97(2):207-215.

46. Yanai J, Pick CG, Rogel-Fuchs Y, Zahalka EA. Alterations in hippocampal cholinergic receptors and hippocampal behaviors after early exposure to nicotine. *Brain Research Bulletin* 1992;29(3-4):363-368.

47. Seidler FJ, Levin ED, Lappi SE, Slotkin TA. Fetal nicotine exposure ablates the ability of postnatal nicotine challenge to release norepinephrine from rat brain regions. *Developmental Brain Research* 1992;69(2):288-291.

48. Slotkin TA, McCook EC, Seidler FJ. Cryptic brain cell injury caused by fetal nicotine exposure is associated with persistent elevations of c-fos protooncogene expression. *Brain Research* 1997;750(1-2):180-188.

49. Leech SL, Richardson GA, Goldschmidt L, Day NL. Prenatal substance

50. exposure: effects on attention and impulsivity of 6-year-olds. *Neurotoxicology and Teratology* 1999;21(2):109-118.

51. Sexton M, Fox NL, Hebel JR. Prenatal exposure to tobacco, II: effects on cognitive functioning at age three *International Journal of Epidemiology* 1990;19(1):72-77.

52. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. *Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency.* Bethesda, MD: US Dept of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute; 1999. *Smoking and Tobacco Control Monograph*; no. 10. NIH Publication No. 99-4645.

53. Cornelius MD, Goldschmidt L, Dempsey D. Environmental tobacco smoke exposure in low income six-year-olds: parent-report and urine cotinine measures. *Nicotine & Tobacco Research* In press.

54. Dolan-Mullen P, DiClemente CC, Velasquez MM, Timpson SC, Groff JY, Carbonari JP, Nicol L. Enhanced prenatal case management for low income smokers. *Tobacco Control* 2000;9(suppl 3):iii75-iii77.

55. Mullen PD, Quinn VP, Ershoff DH. Maintenance of nonsmoking postpartum by women who stopped smoking during pregnancy. *American Journal of Public Health* 1990;80(8):992-994.

56. McBride CM, Pirie PL, Curry SJ. Postpartum relapse to smoking: a prospective study. *Health Education Research* 1992;7(3):381-390.

57. Bauman KE, Flewelling RL, LaPrelle J. Parental cigarette smoking and cognitive performance of children. *Health Psychology* 1991;10(4):282-288.

58. Cornelius MD, Day NL. The effects of tobacco use during and after pregnancy on exposed children: relevance of findings for alcohol research *Alcohol Health and Research World* 2001;24(4):242-249.

59. Eskenazi B, Trupin LS. Passive and active maternal smoking during pregnancy, as measured by serum cotinine, and postnatal smoke exposure, II: effects on neurodevelopment at age 5 years. *American Journal of Epidemiology* 1995;142(suppl 9):S19-S29.

60. Fortier I, Marcoux S, Brisson J. Passive smoking during pregnancy and the risk of delivering a small-for-gestational-age infant. *American Journal of Epidemiology* 1994;139(3):294-301.

61. Mainous AG III, Hueston WJ. Passive smoke and low birth weight: evidence of a threshold effect. *Archives of Family Medicine* 1994;3(10):875-878.

62. Makin J, Fried PA, Watkinson B. A comparison of active and passive smoking during pregnancy: long-term effects. *Neurotoxicology and Teratology* 1991;13(1):5-12.

63. Martin TR, Bracken MB. Association of low birth weight with passive smoke exposure in pregnancy. *American Journal of Epidemiology* 1986;124(4):633-642.

64. Schoendorf KC, Kiely JL. Relationship of sudden infant death syndrome to maternal smoking during and after pregnancy. *Pediatrics* 1992;90(6):905-908.

65. Chilmonczyk BA, Salmun LM, Megathlin KN, Neveux LM, Palomaki GE, Knight GJ, Pulkkinen AJ, Haddow JE. Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. *New England Journal of Medicine* 1993;328(23):1665-1669.

66. Collet JP, Larson CP, Boivin JF, Suissa S, Pless IB. Parental smoking and risk of otitis media in pre-school children. *Canadian Journal of Public Health* 1995;86(4):269-273.

67. Cuijpers CEJ, Swaen GMH, Wesseling G, Sturmans F, Wouters EFM. Adverse effects of the indoor environment on respiratory health in primary school children. *Environmental Research* 1995;68(1):11-23.

68. Douglas RM, Woodward A, Miles H, Buetow S, Morris D. A prospective study of proneness to acute respiratory illness in the first two years of life. *International Journal of Epidemiology* 1994;23(4):818-826.

69. Kandel DB, Wu P, Davies M. Maternal smoking during pregnancy and smoking by adolescent daughters. *American Journal of Public Health* 1994;84(9):1407-1413.

70. Griesler PC, Kandel DB, Davies M. Maternal smoking in pregnancy, child behavior problems, and adolescent smoking. *Journal of Research on Adolescence* 1998;8(2):159-185.

71. Cornelius MD, Leech SL, Goldschmidt L, Day NL. Prenatal tobacco exposure: is it a risk factor for early tobacco experimentation? *Nicotine & Tobacco Research* 2000;2(1):45-52.

72. Miao H, Liu C, Bishop K, Gong ZH, Nordberg A, Zhang X. Nicotine exposure during a critical period of development leads to persistent changes in nicotinic acetylcholine receptors of adult rat brain. *Journal of Neurochemistry* 1998;70(2):752-762.

73. Nordberg A, Zhang X, Fredriksson A, Eriksson P. Neonatal nicotine exposure induces permanent changes in brain nicotinic receptors and behavior in adult mice. *Developmental Brain Research* 1991;63(1-2):201-207.

74. Slotkin TA, Lappi SE, Tayyeb MI, Seidler FJ. Chronic prenatal nicotine exposure sensitizes rat brain to acute postnatal nicotine challenge as assessed with ornithine decarboxylase. *Life Sciences* 1991;49(9):665-670.

75. Rosenberg CE. *The Cholera Years: the United States in 1832, 1849, and 1866.* Chicago: University of Chicago Press; 1962.

76. Fingerhut LA, Kleinman JC, Kendrick JS. Smoking before, during, and after pregnancy. *American Journal of Public Health* 1990;80(5):541-544.

77. Kendrick JS, Merritt RK. Women and smoking: an update for the 1990s. *American Journal of Obstetrics and Gynecology* 1996;175(3 pt 1):528-535.

78. Lillington L, Royce J, Novak D, Rubalcaba M, Chlebowski R. Evaluation of a smoking cessation program for pregnant minority women. *Cancer Practice* 1995;3(3):157-163.

79. Hartmann KE, Thorp JM Jr, Pahel-Short L, Koch MA. A randomized controlled trial of smoking cessation intervention in pregnancy in an academic clinic. Obstetrics and Gynecology 1996;87(4):621-626.