

vitamin B₁₂ levels reflect a disorder of cyanide detoxification. Cyanide is a demonstrable ingredient in cigarette smoke (83, 132, 134, 138, 144, 153, 176).

Vitamin C

Venulet and Danysz (195, 196) have demonstrated that the vitamin C level is significantly lower in the serum of women who smoke cigarettes during pregnancy, compared to values for their nonsmoking counterparts.

Research Issues

Nutrients and oxygen provided by the maternal circulation are essential to normal fetal growth and development. It may be anticipated that some alterations may be produced in the developing fetus when the nutrients are accompanied by toxins in the inhaled smoke of burning tobacco and paper and when carbon monoxide is mixed with the oxygen. Some of the observed alterations may be considered innocuous in themselves, but the evidence to date justifies high priority investigation to determine whether they are indicators of processes that are fundamentally dangerous to either the immediate or long-term health of the fetus and the child.

A number of important questions relating to the possible biological effects of tobacco smoke and its constituents on the fetus *in utero* and the newborn infant remain unanswered. The ethical issue of experiments in pregnant human subjects and newborn infants affects further research. The problems of such studies are obvious but will not be resolved in the foreseeable future. Mathematical models, while useful, require considerable data based on human or animal studies. Models, in addition, possess serious limitations and restrictions because any mathematical abstraction encompasses only a very minute portion of the finite world or a given problem. Thus, future progress in our understanding of the effects of tobacco products in these areas of investigation will require appropriate animal studies with extrapolation to humans.

The research objectives are (1) to identify risk of perinatal loss or damage in women who smoke during pregnancy, and (2) to define the effects on the fetus and the new-born infant resulting from maternally-inhaled tobacco smoke.

In considering the epidemiologic, biologic, and pharmacologic facets of the problem of cigarette smoking and its impact on fetal and infant well-being, the following areas of study are suggested:

Fetal Death

1. Do available data sets confirm the evidence that maternal smoking may lead to anoxic death *in utero* of a normal fetus in an uncomplicated pregnancy?

2. Can the risk of such a death be calculated in terms of the mother's capacity to offset the hypoxic stress of smoking by such mechanisms as increasing hemoglobin or hematocrit; increasing cardiac output; increasing placental ratio, surface area, and area of attachment; or by other mechanisms?

3. Are there indications in existing data sets that anoxic fetal deaths occurred in smoking mothers with, for example, anemia, poor cardiac function, poor pulmonary function, poor general health, unfavorable age (older), or low socioeconomic status?

4. Do these deaths occur more frequently in mothers who, besides being heavy smokers, are anemic or live at high altitudes?

5. Do these deaths occur later in pregnancy when there is less reserve capacity to supply oxygen because of the greater oxygen demand of the larger fetus, the reduction of the placental ratio, and the reaching of the natural limits of increase of hematocrit and cardiac output?

6. Can pregnant women at particular risk of anoxic fetal death if they smoke be identified prospectively by measurement of exhaled CO and carboxyhemoglobin, relating these levels to hematocrit, cardiac output, and other tests of reserve capacity to increase oxygen supply to the fetus?

7. Can pregnant women at particular risk of anoxic fetal death if they smoke be identified by use of exercise testing during prenatal care?

8. Do available data sets confirm the evidence that maternal smoking during pregnancy causes fetal death by increasing the incidence of abruptio placentae, other antepartum bleeding, and related complications?

9. Do available data sets confirm the evidence that the above complications occur more frequently among women with other risk factors such as low socioeconomic status, older age, higher parity, unfavorable previous pregnancy history, and more frequently the more the mother smokes?

10. Are the higher incidences of placental complications and fetal deaths among women who smoke due to poorer diet and lower levels of vitamin C, vitamin B₁₂, folic acid, and other substances that help to maintain tissue integrity?

11. Is there a relationship between the increased incidence of vaginal bleeding in the above cases and the pathological changes in placental blood vessels from smoking women observed by Asmussen?

12. If there is a generalized effect of smoking on the integrity of blood vessel linings and other tissues, what role does this play in the bleeding and abruptio placentae observed in such cases?

13. Can fetal death associated with maternal smoking and placental complications be predicted by careful monitoring of any pregnancy with signs of bleeding after 20 weeks of pregnancy?

14. Can these deaths be prevented by cessation of smoking, supplements of vitamins and folic acid, and other treatment to maintain fetal oxygenation?

Neonatal Death

15. Do available data sets confirm the evidence that maternal smoking leads to neonatal death of otherwise normal babies by increasing the occurrence of preterm birth?

16. What proportion of preterm deliveries of smoking mothers is associated with a history of bleeding early in pregnancy?

17. What proportion of preterm deliveries of smoking mothers is associated with premature rupture of membranes?

18. What is the relationship of maternal smoking to the incidence of bleeding early in pregnancy and of premature rupture of membranes, whether or not there is a preterm delivery and whether or not there is a fetal or neonatal death?

19. Through investigation of characteristics such as age, parity, socioeconomic status, and reproductive history, is it possible to identify women who will be at particularly high risk of pregnancy complications and pregnancy loss if they smoke?

20. Besides the warning sign of bleeding, what other measurements will help to identify the woman who must stop smoking in order to maintain the pregnancy?

21. Will measurement of levels of carboxyhemoglobin, vitamin C, vitamin B₁₂, folic acid, and other indices help to elucidate the mechanisms leading to bleeding and to premature rupture of membranes among smoking mothers?

22. Is there evidence that the tensile strength of fetal membranes is reduced if the mother smokes?

23. Is there evidence that amniotic fluid infection plays a part in the smoking-related increase in the incidence of premature rupture of the membranes?

24. Will elucidation of the mechanisms whereby maternal smoking causes complications of pregnancy, early delivery, and neonatal death help to persuade pregnant women to stop smoking—particularly if they have bleeding early or late in pregnancy—and to persuade obstetricians that cessation of maternal smoking is of crucial importance for a successful pregnancy?

25. Will monitoring of exhaled CO levels in all prenatal care clinics help to reverse the recent trend toward more frequent and heavier smoking among young women?

Spontaneous Abortion

26. Can the increased incidence of spontaneous abortion with maternal smoking be confirmed by further studies, allowing for measurement of dose-response relationships and an accurate estimate of risk ratios?

27. Can the mechanisms of action be worked out, using the same approach as has been done for perinatal mortality?

28. To what extent is a previous spontaneous abortion in a smoker related to a subsequent unfavorable outcome of pregnancy if the woman continues to smoke?

29. Is there an overall increase in the risk of spontaneous abortion as a result of maternal smoking, or is the increased risk confined to women already at risk for other reasons?

Preeclampsia

30. What is the mechanism linking smoking during pregnancy to a reduced incidence of preeclampsia and toxemia?

31. Could components of this mechanism, if understood, be applied so that the risk of preeclampsia could be reduced without incurring the risks associated with smoking?

Sudden Infant Death Syndrome

32. Do existing data sets with postnatal follow-up confirm the association of maternal smoking with an increased risk of SIDS?

33. Do the smoking mothers of SIDS victims have other signs of impairment of their oxygen supply system such as anemia, heart trouble, impaired pulmonary function, or high altitude residence, as indicated in prenatal records?

34. Do the smoking mothers of SIDS victims have early or late bleeding, premature rupture of the membranes, abruptio placentae, or preterm delivery?

Long-Term Follow-Up

35. Can studies with long-term follow-up of growth and development identify groups with smoking-related impairment of a serious nature as opposed to very slight changes in overall means?

36. Could case-control studies using prospective long-term follow-up data (such as that from the British Perinatal Mortality Study) identify maternal smoking patterns and other prenatal factors associated with the problems of physical, intellectual, and emotional development of the children?

Birth Weight and Placenta

37. To what extent does the reduction of birth weight of smokers' babies represent a physiological adaptation to reduced oxygen availability?

38. What are the combined effects on birth weight of maternal smoking, anemia, and high altitude?

39. What are the combined effects of maternal smoking, anemia, and high altitude on weight, shape, area and site of attachment, and placental-fetal ratio?

40. How are these relationships affected by other maternal antecedent factors, such as age, socioeconomic status, and previous history?

41. Is the increased incidence of placenta previa with maternal smoking and high altitude related to an adaptive increase in the placental site of attachment?

42. To what extent do placental changes with maternal smoking represent physiological adaptations to hypoxic and other stresses?

43. To what extent do placental changes represent pathological effects of smoking and what is their role in unfavorable pregnancy outcomes?

Experimental Studies

44. Can experimental studies of exposure to cigarette smoke or to the components of cigarette smoke elucidate the mechanism of reduced birth weight?

45. Is the smoking-associated reduction of fetal growth due to a reduction in the rate of mitosis resulting in a decreased number of cells?

46. Is the smoking-associated reduction of fetal growth rate due to a decreased number of cells in some parts of the body but not in others?

47. Is the smoking-associated reduction of fetal growth rate accompanied by deficiencies in learning ability, emotional development, or physical growth?

Lactation and Breast Feeding

48. Does smoking inhibit milk production in humans? This question could be approached through epidemiological and experimental studies. Surveys of a large population of smoking and nonsmoking women are desirable to correlate the number of cigarettes consumed and the pattern of smoking with the amount of milk produced and the concentration of nicotine and other constituents of smoke in milk throughout the lactation cycle.

49. How does nicotine affect prolactin release, and can this phenomenon be reversed? Appropriate experimental animal research

could provide the basis for understanding mechanism(s) of action and the mapping of appropriate interventions.

50. How much nicotine is excreted in breast milk ingested by the nursing infant? A well-planned pharmacokinetic study should be done involving the mother-infant dyad.

51. Is it possible to determine the complete profile of other components of cigarette smoke in breast milk? The answer to this question will permit the identification of potential carcinogenic agents and their degree of ingestion by the infants.

52. Does the interaction between nicotine and other drugs excreted in breast milk affect the physiology of the infants? The presence of DDT and benzo(a)pyrene, inducers of the activity of drug-metabolizing enzymes, may cause unexpected, subtle side effects in the growing infant which may manifest at a later date.

Tobacco Smoke

53. To what extent does maternal smoking in humans affect maternal and fetal blood catecholamine concentrations?

54. To what extent does maternal smoking affect uterine and placental blood flow?

55. To what extent does maternal smoking affect fetal heart rate, breathing pattern, electroencephalographic activity, or other parameters that can be monitored (that is, dose-response relationships)?

56. To what extent does smoking marijuana differ in its effects on the mother and fetus as compared with smoking tobacco in cigarettes?

57. To what extent are there interactions between the effects of the major (and perhaps minor) components of tobacco smoke?

58. How can efforts to actively discourage smoking during pregnancy be made more effective?

59. To what extent will smoking withdrawal during pregnancy result in changes in infant weight, perinatal mortality, and long-term sequelae?

Nicotine

60. How does nicotine affect ganglionic development in the embryo and fetus?

61. What is the relationship between development of essential hypertension and nicotine imprint on fetal development?

62. Does nicotine accumulation in the fetal adrenal glands, heart, and kidneys modify development of these organs?

63. What is the effect of nicotine on the hormonal systems of the adrenal and those organs regulating adrenal function?

64. To what extent is nicotine accumulation in the fetal kidney involved in a possible antidiuretic hormone abnormality or other complications in later development?

65. What factors are involved in prolonging gestational length in laboratory animals?

66. Since nicotine modulates neurological function in adults at several areas (central nervous system, skeletal-muscular, ganglia, and so forth), how does it modify development and function?

67. To what extent does the effect of nicotine on neurological function contribute to hyperkinetic syndrome in children?

68. What is the potential for nicotine metabolites being carcinogenic in combination with benzo(a)pyrene?

Carbon Monoxide

69. To what extent are embryonic, fetal, or newborn tissues more or less sensitive to the effects of carbon monoxide than those of adults?

70. How does exposure to carbon monoxide physiologically affect the developing fetus or newborn?

71. To what extent do dose-response relationships exist for various carboxyhemoglobin concentrations?

72. Does a "threshold" level result in adverse effects?

73. Does the fetus adapt to low CO concentrations, and if so, by what mechanism?

74. To what extent does CO affect oxygen consumption by the fetus or by individual organs?

75. How does the decrease in blood oxygen tension physiologically affect oxygen availability to the fetal brain, heart, and other vital organs?

76. To what extent do decreases in the mean partial pressures of capillary oxygen affect cellular respiration?

77. How does increased carboxyhemoglobin concentration affect tissue oxygenation?

78. To what extent are the patterns of growth, development, and maturation of the central nervous system and other organ systems interrelated and affected by chronic low-level carbon monoxide exposure?

79. How does carbon monoxide affect developing neuroblasts?

80. To what extent does carbon monoxide increase the risk of prematurity or adversely affect the rate of infant growth?

81. To what extent does the interference with fetal oxygenation result in problems such as mental retardation, cerebral palsy, and perhaps subclinical neurologic, intellectual, or behavioral deficits?

82. Can modifications significantly decrease carbon monoxide levels in tobacco smoke?

83. Do the carbon monoxide concentrations encountered in association with maternal smoking adversely affect the infant's physical or psychomotor development?

84. What are the legal and regulatory considerations concerning the maximum carbon monoxide exposure allowed for pregnant women and newborn infants?

Polycyclic Hydrocarbons

85. To what extent does benzo(*a*)pyrene cross the placenta and enter the fetus?

86. What is its distribution in the fetal organs and tissues?

87. To what extent do the benzo(*a*)pyrene concentrations encountered in smoking mothers affect the growth and development of the fetal brain and other organs?

88. To what extent does benzo(*a*)pyrene have long term effects on the developing embryo and fetus; that is, to what extent are fetuses so exposed subject to the later development of neoplasms or malignancies?

Pregnancy and Infant Health: References

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9. PEPTIC ULCER DISEASE.

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Epidemiology

For over half a century the medical literature has carried reports of an association between peptic ulcer disease (PUD), including gastric ulcer and duodenal ulcer, and cigarette smoking. Barnett (2) in 1927 was the first to examine the epidemiological evidence for this suspected relationship. Although he found that patients with duodenal and gastric ulcer smoked more than controls, the difference was not significant, and he concluded that the purported relationship between smoking and PUD did not exist. However, the majority of subsequent reports have found a significant association between smoking and PUD. Some recent reviews of the older studies (3, 59, 60) present support for the conclusions that (1) the prevalence of smoking is increased in persons with PUD, and (2) both gastric and duodenal ulcers are more prevalent in smokers than in nonsmokers. During the past decade several studies have been published which support these conclusions. These will now be considered.

Prevalence of Smoking in Persons with Peptic Ulcer Disease

Kasanen and Forsstroem (33) studied the stresses and habits of 100 patients with gastric or duodenal ulcer and found that 90 percent of ulcer patients smoked compared to 60 percent of controls and that 61 percent of ulcer patients smoked one or more packs per day as opposed to 36 percent of controls ($p < .01$). Smoking was the only variable significantly related to ulcer in this study, as no relation to stress (financial, work, or family) was found.

Monson (38) studied 10,000 Massachusetts physicians and found that those with gastric or duodenal ulcers smoked significantly more than comparable control subjects. About 1.3 times as many duodenal ulcer patients as control subjects smoked. He did not find a difference between PUD patients and controls in years of smoking or in number of packs per day smoked.

In a Danish study (32), 78 percent of PUD patients smoked compared to 71 percent among controls, a difference which was not statistically significant. Bock (6), in a South African study, found that 89 percent of men and 45 percent of women with gastric ulcer smoked, but he did not study a control group.

Doll (18), who has written extensively on the subject of smoking and ulcer disease (17, 19), found a significantly increased frequency of smoking in both duodenal and gastric ulcer patients as compared to controls: gastric ulcer—91 percent smokers, control—79 percent smokers; duodenal ulcer—85 percent smokers, control—81 percent smokers ($p < 0.01$).

Although there is some problem in determining the adequacy of controls in these studies, all five in which controls as well as ulcer

patients were studied (6, 19, 32, 33, 38) show a higher proportion of smokers among ulcer patients than among controls.

Prevalence of Peptic Ulcer Disease in Smokers

We turn now to studies of the prevalence of PUD among smokers and nonsmokers, which are described below and summarized in Table 1.

Edwards and coworkers (22) examined 1,753 men over age 59 in regard to smoking and health. A history of peptic ulcer was present in 6.0 percent of nonsmokers and in 10.0 percent of cigarette smokers ($p < .01$). Also, the prevalence of peptic ulcer increased with increasing number of cigarettes smoked daily.

Higgins and Kjelsberg (28), in a large community health study in Tecumseh, Michigan, discovered a greater frequency of peptic ulcer in male and female smokers and ex-smokers than among nonsmokers (the increased frequency reached statistical significance only in women).

The interrelationships among coffee, alcohol, and smoking were examined by Friedman, et al. (23). They studied 36,656 men and women, aged 30 to 59, 2,597 of them with a history of peptic ulcer disease. They found that men who smoked had a 2.1-fold greater frequency of ulcer disease than those who did not smoke, and women had a 1.6-fold greater frequency. The degree of smoking was evaluated by looking at three variables: quantity, years of smoking, and inhalation; all showed positive relationships with the frequency of PUD. On the other hand, since neither coffee drinking nor alcohol consumption was related to an increased occurrence of peptic disease, they concluded that the association of cigarette smoking with PUD is independent of any possible association between smoking and alcohol or coffee consumption.

Similar results were found in a study of 4,000 Polish men and women (31) in which the prevalence of PUD was evaluated. Among men, ulcers were found with greater frequency in smokers and ex-smokers than among nonsmokers; and, among smokers, the prevalence of ulcers was greater in those persons who had smoked for more than 5 years and in those smoking more than 14 cigarettes per day. Women smokers did not show an increased frequency of PUD, but only 7 percent of those studied were current smokers. Among women smokers, however, PUD prevalence was higher for those with a longer smoking history and for heavier smokers. On the other hand, in a study of 402 Czechoslovakian men with PUD (43), smoking did not make a strong contribution to a stepwise regression predicting the presence of PUD (the data were not provided in the paper and therefore could not be included in Table 1).

In the only truly prospective study (41), a 16- to 50-year follow-up study using smoking history in college, PUD was found in 2.2 percent of those who smoked in college as opposed to 1.5 percent of

TABLE 1.—Peptic ulcer prevalence in smokers and nonsmokers (no. per 100)

Reference	How diagnosed	No. with ulcers	Rates: age-adjusted	Sex	Current cigarette smokers	Non-smokers	Ratio	Dose-response
Edwards, F. (1959) (22)	Doctor	143	no	M	10.1	6.0	1.7 ^a	yes
Higgins, M.W. (1966) (28)	Doctor	140	yes	M	7.1	5.2	1.4	—
		47	yes	F	2.8	1.4	2.0	—
Friedman, G.D. (1974) (23)	History	1520 ^b	yes	M	12.2	5.8	2.1 ^c	yes
		1092 ^b	yes	F	6.3	3.9	1.6	yes
Jedrychowski, W. (1974) (31)	Doctor	106 ^b	no	M	6.4	1.9	3.4	yes
		26 ^b	no	F	.8	1.3	.6	yes
Paffenbarger, R.S. (1974) (41)	History	389	yes	M	2.2 ^d	1.5 ^d	1.5 ^d	yes
Goldbourt, U. (1975) (25)	X-ray	895	no	M	10.2	6.2	1.6	no

^aAlso, ratio > 1 within age and social class.

^bNot given - estimated, using total population and reported rates.

^cAlso, ratio > 1 within occupational groups.

^dSmoking categories in college, ulcers developed in 16 to 50 year follow-up.