These studies suggest unfavorable effects of maternal smoking during pregnancy on the child's long-term growth, intellectual development, and behavioral characteristics. Although these changes are difficult to study because of the vast complexity of possible antecedent and confounding variables, high priority should be given to obtaining conclusive answers about the role of fetal exposure to maternal smoking in these conditions. The fact that the direction of observed differences in a variety of different studies is the same adds to the urgency of this question.

Role of Maternal Weight Gain

In the search for mechanisms through which maternal smoking reduces birth weight, the question has been asked whether it might be an indirect result of reduced appetite, less intake of food, and lower maternal weight gain. Several early studies reported no differences between smoking and nonsmoking women in intake of food or in weight gain and concluded that the effect of maternal smoking on birth weight was not mediated in this way (*8, 54, 76, 101, 141, 212*). Recently the question has been raised again by Rush in a study of births to 160 women of whom 41 smoked throughout pregnancy. His evidence showed that the mean weekly weight gain was reflected in the infant's weight at birth (*162*). In a subsequent study, Davies, et al. examined the interrelationships of cigarette smoking in pregnancy, maternal weight gain, and fetal growth. By analysis of covariance of 480 mother-infant pairs from the total of 1,159 included in the study, these authors stated: "Correction of birth weights within smoking groups to a common mean maternal weight gain appears to remove most of the differences between infants of nonsmokers and heavy smokers, although technically these corrected means are still statistically heterogeneous." That is, the effect of smoking on birth weight was still observed although diminished by these procedures. From this the authors concluded that "a large part of the effect of maternal smoking is mediated through maternal weight gain with only a very small additional direct effect on the fetus. This suggests that increasing weight gain in smoking mothers might prevent some of the harmful effects of smoking on fetal growth." However, the alternative explanation that lower maternal weight gain and fetal growth retardation are both independently related to cigarette smoking in pregnancy is also mentioned (*34*).

Other studies have not corroborated these findings. Mau reports results of the German prospective study in which 6,200 pregnant women were examined every month from the first trimester to delivery and the children followed for up to three years. Smoking was classified as none, 1 to 5, 6 to 10, or more than 10 cigarettes per day. No significant association was found between smoking habit and weight gain. On the other hand, there was a close correlation between the

number of small-for-dates babies and the smoking habit in a subgroup of women with normal weight gain (10 to 15 kg). The proportions of babies below the tenth percentile were 7.7 percent for nonsmokers, 8.4 percent at 1 to 5 cigarettes, 12.5 percent at 6 to 10, and 17.6 percent at over 10 cigarettes per day. These babies had a general retardation of weight, length, and head circumference rather than appearing malnourished (*107*). These findings are in agreement with the studies of Miller and Hassanein, who found that the effects of smoking on fetal growth did not appear to be related to poor maternal nutrition. Mean weight gains during the last two trimesters of pregnancy were not significantly different in smoking and nonsmoking mothers and were above the mean weight gains recommended by the National Research Council (*118*).

Meyer investigated the relationship of maternal smoking to maternal weight gain and to birth weight, using data from the 31,788 births to English-speaking Canadian-born women included in the Ontario Perinatal Mortality Study (*113, 142, 143*). As expected, birth weight distributions shifted downward as maternal smoking level increased. Maternal weight-gain distributions, on the other hand, were the same for smokers and nonsmokers. Furthermore, the proportion of infants weighing less than 2,500 grams increased with each level of smoking (none, less than a pack, and more than 1 pack per day) within each maternal weight-gain group from less than 5 pounds to more than 40 pounds. This evidence supports a direct effect of maternal smoking on birth weight rather than one mediated through eating. Evaluation of Rush's study (*162*) is difficult because of small numbers and because of population-selection factors that led to large differences between smokers and nonsmokers in age, parity, marital status, and education. The study population of Davies, et al. (*34*) is more homogeneous and contains 450 smokers, but both studies share a common problem in interpretation. Meyer points out that an inevitable correlation exists between maternal weight gain and birth weight insofar as both increase with gestational age, necessitating careful control of this factor. Furthermore, the fact that fetal weight is an increasingly important component of maternal weight gain towards term (51 percent between 30 and 40 weeks) and accounts for a larger proportion of a low-weight gain than of a high-weight gain ensures a considerable degree of correlation between the two values. The same baby is weighed twice, once while growing *in utero* and contributing to maternal weight gain, and again at birth. In this way the mother gains weight because the baby is growing, and not vice versa. Meyer concludes that efforts to prevent or reduce smoking during pregnancy should have greater benefits for mother and child than would efforts to increase food intake among women who smoke (*113*).

Evidence for Indirect Associations Between Smoking and Birth Weight

Yerushalmy has suggested that smoking is an index to a particular type of reproductive outcome and does not play a causal role in the production of small-for-dates infants (*206-208*). The line of reasoning and evidence presented by Yerushalmy and the responses to it are discussed in detail in the 1973 report on *The Health Consequences of Smoking* (*192*). The problems inherent in Yerushalmy's study, in which he found a higher percentage of low birth weights among 210 nonsmokers who later became smokers than among nonsmokers who did not take it up, have been described. The most serious of these problems is the bias introduced by the study design resulting in significantly younger ages for the "future smoker" group (mean age 19.70 ± 0.15) than for his nonsmokers (22.10 ± 0.04); the doubly retrospective nature of the information gathered (women being asked about smoking habits at the time of previous pregnancies); and lack of control for other important factors influencing birth weight, such as primiparity and sex of child.

Silverman addressed the question of whether the smoker rather than the smoking was responsible for increased frequency of low birth weight by comparing pairs of births to the same woman, using data from the 1963 private census of the population of Washington County, Maryland (*28*). In this census all members of the household were listed with birth dates, and all members were asked whether and how much they smoked and when they had started. Using these data, Silverman constructed a population of pairs of births that occurred during the 17-year period prior to the census date of July 15, 1963. Assuming that the mothers did not stop smoking during pregnancy and that the age of starting was accurately reported, she was able to compare birth weights in first and second births of 143 women who smoked during the second pregnancy, but not during the first, with corresponding birth weights from 382 women who smoked during neither pregnancy and 491 women who smoked during both pregnancies. The many problems inherent in this study were faced, and adjustments were made insofar as possible. For example, as in Yerushalmy's study, significantly more of the future smokers (44.8 percent) were under 20 years of age at the time of the first study birth, compared with 24.5 percent of the continuing nonsmokers. Young, primiparous mothers are known to have lighter babies than older mothers with higher parity. When weights were compared specific for maternal age and sex of child, the mean birth weight for the first member of the birth pair was lower in four out of six comparisons and higher in two. With simultaneous adjustment for the effects of infant sex, maternal age, and birth order, there were no significant differences in mean birth weight difference among pairs in which the mother smoked during both pregnancies and pairs in which the mother smoked during the

second pregnancy of the pair, but not the first. Comparison of the mean birth weights for the first infants in each pair showed that future smokers had babies who weighed less than those of women who did not take up smoking and more than those of women who were already smokers and continued to smoke. Silverman concluded: "These findings neither confirm nor deny the hypothesis that the smoker rather than the smoking per se causes a reduction in birthweight" (*171*).

Evidence for a direct effect of maternal smoking on fetal growth as presented in this chapter is extremely strong. Furthermore, the biological effects of carbon monoxide, nicotine, and other known components of cigarette smoke are compatible with the findings from epidemiologic studies. Therefore, there seems little value in arguing that this direct effect does not exist. On the other hand, smokers are to some extent self-selected, and comparisons of "smokers" and "nonsmokers" in a population reveal differences between them. These may be related to calendar time trends, peer group influence, cultural and ethnic background, social class, or personality type. Because the relationship between maternal smoking and birth weight is so strong, these differences do not obscure it. More problems arise from lack of adjustment for differences between smokers and nonsmokers in the distribution of such factors as age, parity, socioeconomic status, and race when the relationship of maternal smoking to perinatal mortality is under study; these issues are discussed in detail in another section of this chapter. In addition, attention should be paid to the possibility that psychological makeup and strength of addiction to cigarette smoking may have an independent influence on some of the outcomes being studied. Future studies should not only adjust for independent factors that influence whether or not a woman becomes a smoker and smokes during pregnancy but should also distinguish between the effects of a personality type that adopts smoking and the physical effects of the smoke on mother, placenta, and fetus.

Summary

1. Babies born to women who smoke during pregnancy are on the average 200 grams lighter than babies born to comparable women who do not smoke. The whole distribution of birth weights of smokers' babies is shifted downward, and twice as many of these babies weigh less than 2,500 grams compared with babies of nonsmokers. There is abundant evidence that maternal smoking is a direct cause of the reduction in birth weight.

2. Birth weight is affected by maternal smoking independently and to a uniform extent, regardless of other determinants of birth weight. The more the mother smokes, the greater the reduction in birth weight of the baby.

3. The ratio of placenta weight to birth weight increases with increasing levels of maternal smoking. This increase may signify a response to reduced oxygen availability due to carbon monoxide and may have some survival value for the fetus.

4. There is no overall reduction in the duration of gestation with maternal smoking, indicating that the lower birth weight of smokers' infants is due to retardation of fetal growth.

5. The pattern of fetal growth retardation that occurs with maternal smoking is a decrease in all dimensions: body length, chest circumference, and head circumference are smaller if the mother smokes. Smokers' babies are short for dates as well as light and do not exhibit reduction in ponderal index.

6. Studies of long-term growth and development give evidence that smoking during pregnancy may affect physical growth, mental development, and behavioral characteristics of children at least up to the age of 11.

7. Overwhelming evidence indicates that maternal smoking during pregnancy affects fetal growth rate directly, that fetal growth rate is not due to characteristics of the smoker rather than to the smoking nor mediated by reduced maternal appetite, eating, and weight gain.

Cigarette Smoking and Fetal and Infant Mortality

Overview

In contrast with the strong, consistent relationship of maternal smoking to reduced birth weight, the relationship of maternal smoking to perinatal mortality has been marked by variation in the level of increased risk for women who smoke. This has led to controversy as to whether there truly are lethal effects for the fetus or neonate caused by maternal smoking.

Earlier epidemiological studies of the association between maternal cigarette smoking and perinatal mortality (fetal deaths, neonatal deaths, or perinatal deaths) were reviewed in the 1971, 1972, and 1973 reports on *The Health Consequences of Smoking* (*190–192*). The 1971 report gave details of 12 studies of maternal smoking and the incidence of spontaneous abortion, stillbirth, and neonatal death (*20, 41, 54, 87, 101, 141, 151, 164, 166, 188, 206, 212*). The increased risk of loss among smokers varied from study to study. Inconsistencies between studies were described, and it was noted that both smoking habits and perinatal loss were influenced by such factors as social class, maternal age, and parity. Rush and Kass reviewed the English language literature in 1972 and found reports of 12,388 perinatal deaths and abortions with a mean excess perinatal loss for smokers of 34.4 percent. Where reported, excess loss was higher among the poor and among blacks. Their study of black and white women in Boston showed excess

mortality risks of 86 percent for black smokers and 11 percent for white smokers (*163*).

The 1973 report (*192*) summarized studies that were published up to that date and contained a critical analysis of known reasons for variability in the strength of the association between maternal smoking and increased perinatal loss. Much of the controversy about whether maternal smoking did or did not cause fetal or neonatal loss centered around the basically irrelevant issues of whether studies were "prospective" or "retrospective" (usually referring to the time at which smoking information was obtained rather than to whether the study was based on a cohort of births or on a set of cases and controls), and on whether or not the differences were "statistically significant." Classification of the studies reviewed in the 1973 report according to statistical significance revealed that studies in which the higher rates of mortality for the infants of smokers compared with nonsmokers reached a significant level (usually $p \leq 0.05$ or smaller) (*20, 22, 30, 54, 86, 89, 124, 142, 143, 165, 180*) had mortality ratios (smoker rate: nonsmoker rate) that ranged from 1.38 to 1.78, whereas studies in which significant levels were not reached (*41, 141, 151, 155, 166, 189, 207*) had mortality ratios that ranged from 1.01 to 1.06. Both groups contained retrospective and prospective studies of comparable size. Statistical significance obviously depended upon the combined effects of the risk ratio and the size of the study. A further source of controversy in this matter was the fact that when one compares neonatal death rates for low-birth-weight babies only, the low-weight babies of smokers have lower death rates than those of nonsmokers. This apparently paradoxical relationship is partly due to the relatively greater maturity of the under-2,500-gram smokers' babies. It is also due to the fact that maternal smoking affects birth weight more strongly than it does neonatal mortality. Because the denominators of these rates include only babies under 2,500 grams, the downward shift of birth weight with maternal smoking inflates the denominators and lowers neonatal mortality rates for smokers. Numerators include a majority of low-birth weight babies, whether or not the mother smokes. This matter is discussed more fully in the 1973 report (*192*) and in the commentary by Meyer and Comstock (*114*).

In the 1973 report, analysis of reasons for variability between studies included two important points. First was the observation that other important variables might influence the results if they were unequally distributed in comparison groups of smokers and nonsmokers. A logistic transformation analysis of variance applied to data from the British Perinatal Mortality Study demonstrated that in addition to maternal smoking, maternal height, age, parity, social class, and severe preeclampsia had significant independent effects on late fetal and neonatal mortality (Figure 5). Meyer and Comstock (*114*) provided examples of how the differential distribution of smoking and other

factors could bias data. For example, as reported in the data from the Collaborative Perinatal Study of the NINCDS (1959–1966), U.S. mortality rates were higher for black than for white babies, while white women were more often smokers and smoked more cigarettes than black women (*137*). Selection of births on the basis of smoking alone would tend to include more nonsmokers who were black and at high risk and more smokers who were white and at basically low risk, thereby minimizing the apparent effects of maternal smoking on perinatal loss. In three reported studies in which adjustment for other factors was carried out, a significant independent association between cigarette smoking and infant mortality persisted (*20, 22, 30, 169*). Of the studies that revealed no significant increase in mortality risks for smokers' infants, one (*207*) controlled for race alone. "Hence, at least part of the discrepancy in results between the two groups of studies may be explained by a lack of control of variables other than smoking" (*192*).

The second important point presented in the 1973 report was the suggestion that cigarette smoking might be more harmful to the fetuses of certain women than of others. Analysis of data by socioeconomic status (*2, 22, 29*), race (*137, 163, 188, 206, 207*), previous obstetrical experience (*22, 151, 169*), and maternal age (*20*) indicated that the increased perinatal mortality risk associated with maternal smoking varied considerably with these other factors (*192*).

Spontaneous Abortion

The results of several past studies have demonstrated a statistically significant association between maternal cigarette smoking and spontaneous abortion (*74, 89, 141, 147, 188, 212*). Data from some of these studies have documented a strong dose-response relationship between the number of cigarettes smoked and the incidence of spontaneous abortion (*147, 188, 212*). Spontaneous abortions are difficult to study because of problems in ascertainment. The most complete ascertainment is possible when the mother's history of past spontaneous abortions is used, despite problems of recall. Differences in rates between smokers and nonsmokers are largest when this method is used (*141, 212*). In prospective studies, many early spontaneous abortions will be missed, and bias will occur if one group tends to register earlier than the other. Nevertheless, higher rates of spontaneous abortion are also reported among smoking mothers in prospective studies (*89*). The study by Kullander and Kaellen counted spontaneous abortions through the eighth month of gestation and noted that the largest increase was among smoking women whose pregnancies were unwanted. Although this was a prospective study, with smoking data collected repeatedly during prenatal care, the method of analysis was retrospective. Rearrangement of their table to

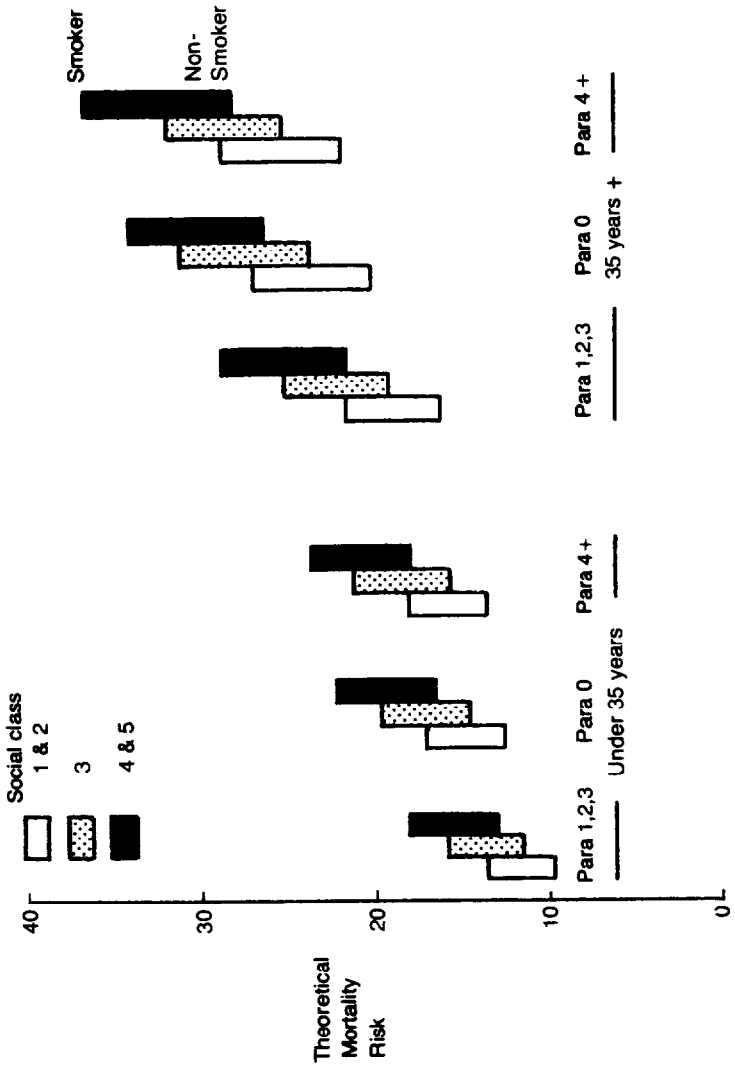

FIGURE 5.—Theoretical cumulative mortality risk according to smoking habit, in mothers of different age, parity, and social class groups

SOURCE: Butler, N.R. (*20*).

obtain incidence rates of spontaneous abortion for subgroups of smokers and nonsmokers gives rates and relative risks of spontaneous abortion by desideration of pregnancy (Table 4). More of the smokers' than nonsmokers' pregnancies were unwanted (19 percent versus 13

TABLE 4.—Spontaneous abortions by maternal smoking habit and desideration of pregnancy

	Spontaneous abortions per 100 pregnancies		Smoker: nonsmoker Relative risk
	Smokers	Nonsmokers	
Total spontaneous abortions	9.4	7.2	1.31
Pregnancy wanted	7.8	6.5	1.20
Pregnancy unwanted	16.0	11.9	1.34

SOURCE: Kullander, S. (*89*).

percent), but the increased risk of spontaneous abortion was seen among smokers whether or not the pregnancy was wanted (*89*).

The method for studying spontaneous abortions that may be the least subject to error if carefully done is the traditional, retrospective, case-control approach, used recently by Kline and coworkers (*87*). In their study a log-linear analysis was used to test the hypothesis that maternal smoking is associated with spontaneous abortion, controlling for confounding variables such as age, number of previous spontaneous abortions, induced abortions, and live births. Of the cases of spontaneous abortion, 41 percent were smokers compared with 28 percent of the controls, giving an odds ratio of 1.8. This leads to the conclusion that smoking during pregnancy is a risk factor for spontaneous abortion.

Perinatal Mortality

Most of the epidemiological studies about which questions of causality have arisen have used perinatal death (late fetal and early neonatal), neonatal death, or combinations of these as their outcome variable. Ascertainment and recordkeeping may start at 20 weeks, at 28 weeks, or at the time of registration. These differences in definition and design affect the study results but are not fundamental to the basic questions raised in the 1973 report and by other authors.

Progress toward resolving these questions has been made since the 1973 report through new studies and analyses in which attention is paid not only to differences in the number of cigarettes smoked but also to other characteristics of the study populations. A table from Fabia's study of a 10 percent random sample of registered births in Quebec in 1970-71 illustrates this approach (Table 5). Within subgroups of the population by maternal age, parity, and years of school, the relative perinatal mortality risk for smoking versus nonsmoking mothers varies from 1.00 to 1.81 for categories with at least 10 deaths (*47*). Table 6 (*117*) shows examples of a number of studies in which

TABLE 5.—Perinatal mortality rates per 1,000 live births to smoking and nonsmoking mothers, and relative risks for infants of smokers by maternal age, parity, and years of school (10 % random sample of medical certificates of births in Quebec in 1970–71)

Maternal characteristics	Total births	Perinatal deaths per 1,000 live births		Smoker: nonsmoker Relative risk
		Nonsmokers	Smokers	
Age				
< 25	3,143,	12.1	16.1	1.33
25-34	3,717	12.6	13.2	1.05
35+	757	23.0	41.7	1.81
Parity				
0	2,798	14.2	18.7	1.32
1-3	3,959	11.2	11.2	1.00
4+	860	21.8	36.1	1.66
Years of school				
< 8	1,600	14.5	18.8	1.30
8-11	3,043	12.8	19.7	1.54
12+	1,170	13.5	(8.9)	(0.66)

Excludes births weighing less than 1,001 grams.
Rates in parentheses based on fewer than 10 deaths.
SOURCE: Fabia, J. (*47*).

perinatal mortality rates by maternal smoking are shown within categories of other relevant factors. These studies show that perinatal mortality rates vary with maternal smoking level and also with the other factors shown. The general statement can be made that the detrimental effect of maternal smoking on fetal survival is greater in groups of women who already have a higher risk of perinatal loss for other reasons. Women characterized by low social class, low level of education, less than optimum maternal age, or being black have higher risks of perinatal mortality than their counterparts, and their relative increase in risk due to maternal smoking is enhanced. Studies in which the population, by design or by chance, includes mainly or only women without other reproductive risk factors show the smallest differences between the risks of smokers and nonsmokers (*22, 30, 47, 137, 155, 163, 206*).

A series of articles by Meyer, et al. reports analyses of data from the Ontario Perinatal Mortality Study of all single births in 10 Ontario teaching hospitals in 1960-61, including 51,490 births, 701 fetal deaths, and 655 neonatal deaths (*115, 116, 117*). For the Ontario study, sponsored and supported by the Maternal and Child Health Branch of the Ontario Department of Health (*142, 143*), detailed data were

TABLE 6.—Examples of perinatal mortality by maternal smoking status related to other subgroup characteristics

Study population	No. of births		Category	Perinatal or neonatal deaths/1,000 births		Relative risk*
	Non-smokers	Smokers		Non-smokers	Smokers	
British Perinatal Mortality Survey, England, all births	11,145	4,660	Social class			
			1,2 (high)	25.8	26.3	1.02
			3–5	33.5	46.6	1.39
Washington Co. Maryland, white	7.646	4.641	Father's education			
			9+ years	14.4†	16.1†	1.12
			≤8 years	17.6†	38.0†	2.16
Northern Finland, white	8.898	2.346		23.2	23.4	1.01
California, middle to upper middle class			Race			
	6,067	3,726	White	11.0†	11.3†	1.03
	2,219	1,071	Black	17.1†	21.5†	1.26
Boston City Hospital, Prenatal Clinic			Race			
	513	892	White	29.2	31.4	1.08
	1,225	636	Black	28.6	54.1	1.89
Collaborative Perinatal Study, 12 U.S. centers			Race and cigarettes/day			
	8,521	11,369	White	31.4		
			1–10		31.5	1.00
			11+		38.2	1.22
	9,862	8,160	Black	38.5		
			1–10		41.5	1.08
			11+		57.4	1.49
Quebec, 10% sample of registered births	3,912	2,967	Maternal age			
			<25	12.1	16.1	1.33
			25–34	12.6	13.2	1.05
			35+	23.0	41.7	1.81

*Ratio of mortality rate for smokers' to nonsmokers' babies.
†Neonatal only.
SOURCE: Meyer, M.B. (*117*).

collected from routine records, and from interviews with mothers, anesthetists, and attending physicians, and from autopsy records. Results related perinatal mortality to social, demographic, and physical maternal factors, prenatal care, histories of prior pregnancies, complications of pregnancy, details of anesthesia, delivery, hospital course, and survival of the infant up to 8 days. The interviews of

mothers included questions on the maximum amount smoked during pregnancy, expressed as packages per day (*142, 143*). The large size of this study and the richness of its available information provided a valuable resource for sorting out complex interrelationships between maternal smoking, other factors, and perinatal loss. In the first article of the series, the differential risk of smoking based on maternal characteristics was demonstrated by extensive cross-tabulation of perinatal mortality rates for 3 levels of smoking (none, less than a pack, 1 pack or more per day) within 52 subgroups of other maternal variables. Risk ratios for light smokers compared with nonsmokers showed excess death risks of less than 10 percent for women of young age, low parity, and normal hemoglobin. At the other extreme, mothers of high parity, public hospital status, with previous premature infants, or with hemoglobin under 11 grams and who were heavy smokers (one pack or more per day) had increased perinatal mortality risks of 70 to 100 percent. Risks for light smokers who had other antecedent risk factors and for heavy smokers with otherwise good prognosis fell between these extremes when compared with nonsmokers. These relationships show how selection of a study population from one end or the other of this spectrum of smoking-associated risk levels would influence the relative risk found for smoking when no adjustment is made for these other factors (*117*). Other studies in which similar cross-tabulations have been made between maternal smoking level and socioeconomic level, maternal age, parity, previous pregnancy history, and other such factors have corroborated these findings (*2, 22, 29, 47, 102, 169*).

Because of possible interactions between maternal smoking and the other independent variables, Meyer, et al. undertook further analysis of the Ontario data to define and measure the independent effect of maternal smoking on the risk of perinatal mortality. For this a multiple regression analysis was used to compare the relative importance of smoking and other factors in their influence on perinatal mortality and on the frequency of low birthweight, of preterm delivery, and of placental complications (*115*). When the rates of perinatal mortality by smoking were adjusted for the effects of all other factors, perinatal mortality rates per thousand births were 23.5 for nonsmokers, 28.2 for smokers of less than a pack per day, and 31.8 for smokers of a pack or more per day. In other words, light smoking increased the risk by 20 percent and heavy smoking increased it by 35 percent. This is a highly significant, dose-related, independent effect, but it is less strong than the relationship to perinatal mortality of hospital pay status (a 55 percent increase for public status mothers), age-parity differences, or a history of previous pregnancy loss (190 percent greater risk if there is a previous loss compared with primiparity or with a previous pregnancy with no fetal or neonatal loss) (*115*).

TABLE 7.—Cause of stillbirth related to smoking habit

Cause of stillbirth	Percentage incidence	
	Nonsmokers	Smokers
Maternal disease	0.01	—
Maternal hypertension	0.19	0.17
Difficult labour	0.09	0.05
Antepartum hemorrhage	0.11	0.39
Congenital malformation	0.32	0.27
Haemolytic disease	—	0.13
Infection	0.01	—
Anoxia (without obvious cause)	0.24	0.23
Other cause stillbirth	—	0.02
Macerated stillbirth (without obvious cause)	0.29	0.23
Total stillbirths	1.30	1.54

SOURCE: Andrews, J. (2).

Cause of Death

The weight of evidence presented in this chapter clearly indicates that maternal smoking does increase the risk of spontaneous abortion, early and late fetal death, and early neonatal death. This being so, it is appropriate to attempt to identify mechanisms of action and intermediate pathways between the cigarette smoke and the fatal event. Clues to these mechanisms might be found if certain causes of death showed an excess among the infants of smoking mothers. Several authors have reported cause-specific mortality rates for the infants of smokers and nonsmokers. Andrews and McGarry (*2*) reported stillbirth rates of 1.30 per 100 births for nonsmokers and 1.54 per 100 for smokers, among which 0.11 and 0.39 were due to antepartum hemorrhage for nonsmokers and smokers respectively. For neonatal deaths, causes showing excess rates for infants of smoking mothers were "immaturity (no other cause)," "respiratory distress syndrome," and "pneumonia," with overall rates of 1.10 and 1.40 for nonsmokers, and smokers, respectively (Tables 7 and 8). Comstock, et al. (*30*) compared observed neonatal deaths of smokers' babies with numbers of deaths expected at nonsmoker rates. Out of 100 total observed deaths, smokers' infants had excesses of 17 due to immaturity, 15 due to asphyxia and atelectasis, and 7 due to birth injuries, with deficiencies of -7 due to congenital defects and -4 due to "other," leaving a net excess of +28. In the prospective study of 9,169 pregnancies carried out by Goujard, et al. (*63*), causes of stillbirth that increased significantly with maternal smoking were "abruptio placentae" ($p = .005$) and "unknown cause" ($p = 0.0005$). Overall differences in stillbirth rates showed an excess for smokers at a significance level of $p = 0.0001$ (Table 9).

TABLE 8.—Cause of neonatal death related to smoking habit

Cause of neonatal death	Percentage incidence	
	Nonsmokers	Smokers
Immaturity (no other cause)	0.25	0.36
Congenital malformation	0.33	0.31
Pneumonia	0.06	0.19
Asphyxia-atalectasis	0.17	0.12
Birth injury	0.03	0.09
Infection	0.03	—
Haemolytic disease	0.01	0.03
Respiratory distress syndrome	0.09	0.16
Other	0.11	0.12
Total neonatal deaths	1.10	1.40

SOURCE: Andrews, J. (*2*).

TABLE 9.—Stillbirths according to cause in relation to maternal smoking during pregnancy

Stillbirths	Number of deliveries	% of smokers	Comparison with live births †
Cause of death:			
Vascular	8	25%	
Abruptio placentae	13	46%	p=0.005
Mechanical cause	13	15%	
Miscellaneous (syphilis, Rh, *malformations*)	24	13%	
Unknown cause	37	35%	p=0.0005
Detailed records not available	5	—	
Total	100	26%	p=0.0001
Livebirths	9069	12%	

†When p is not given, the difference is not significant.
SOURCE: Goujard, J. (*63*).

Meyer and Tonascia (*116*) have analyzed fetal and neonatal deaths from the Ontario Perinatal Mortality Study (*142, 143*) to identify causes of death that show an excess if the mother smokes and to examine the relationship of these deaths to complications of pregnancy and labor. Fetal and neonatal deaths by coded cause and maternal smoking habit are shown in Table 10. For each cause the observed numbers for smokers were compared with the number expected at nonsmoker rates. The differences between observed and expected numbers indicate the number of deaths in each category attributable to maternal smoking. Significance levels of the differences between smoker and nonsmoker rates, based on the null hypothesis of no difference, are shown for p values of 0.06 or less.

TABLE 10.—Fetal and neonatal deaths by coded cause and maternal smoking habit (English speaking mothers)

Coded cause	Observed		Expected smoker*	Observed-expected difference	*P* value†
	Nonsmoker	Smoker			
Fetal deaths					
Unknown	75	125	81.4	43.6	0.003
Malformations	32	24	34.7	-10.7	N.S.
Hemolytic disease	11	15	11.9	3.1	N.S.
Anoxia	16	29	17.4	11.6	N.S.
Maternal cause	31	45	33.7	11.3	N.S.
All others	8	13	8.7	4.3	N.S.
Total	173	251	187.9	63.1	0.003
Neonatal deaths					
Unknown	52	51	56.5	-5.5	N.S.
Malformations	22	24	23.9	0.1	N.S.
Hemolytic disease	7	8	7.6	0.4	N.S.
Respiratory difficulty	46	63	50.0	13.0	N.S.
Prematurity alone	33	65	35.8	29.2	0.005
Maternal cause	2	6	2.2	3.8	N.S.
All others	16	16	17.4	-1.4	N.S.
Total	178	233	193.3	39.6	0.06
Total births	15,240	16,549			

N.S. = Not significant.
*Based on nonsmoker rate.
†P value derived from chi square based on a null hypothesis of no difference between smokers and nonsmokers.
SOURCE: Meyer, M.B. (*116*).

For fetal deaths, the largest category of coded cause was "unknown," and by far the largest and most significant smoking-related difference fell in this category ($p=0.003$). Smokers also showed more than expected fetal deaths due to anoxia and maternal causes and fewer deaths than expected due to malformations. In other categories only minor mortality rate differences were found between the two groups. For neonatal deaths the largest cause of death category was "unknown," but here there was no excess for smokers' infants. Most of the smoking-related excess of neonatal deaths was among those attributable to prematurity alone ($p=0.005$), with additional numbers in the related category of "respiratory difficulty." Differences between observed and expected deaths in other categories were negligible.

The tentative conclusion to be drawn from these findings is that many of the excess fetal deaths associated with maternal smoking do not have any recognizable pathology but occur from otherwise unknown causes. A significant excess also occurs as a result of antepartum hemorrhage or abruptio placentae. The excess neonatal deaths among the infants of smokers appeared to be due to prematurity and to related respiratory problems. In other words, these

deaths occurred in babies who were born preterm, but were without other pathology. There is no convincing evidence that maternal smoking increases the incidence of congenital malformations. Results of published studies, reviewed in the 1973 report, show relative risks for smokers versus nonsmokers ranging from 0.31 to 1.55 (*192*).

Complications of Pregnancy and Labor

Observations from the Ontario study and other data showed that women who smoked during pregnancy had excess fetal deaths either unexplained or attributed to anoxia and excess neonatal deaths due to premature delivery. These findings suggested that maternal smoking might increase the risk of certain pregnancy complications that were related, in turn, to these causes of perinatal loss. A direct relationship between maternal smoking level and the incidence of placenta previa, abruptio placentae, bleeding during pregnancy, and premature rupture of membranes had been reported previously (*2, 31, 63, 115, 189*). Underwood, et al., found higher rates for smokers than for nonsmokers of bleeding, abruptio placentae, and placenta previa combined, and of premature rupture of membranes in three groups of women with different socioeconomic and racial backgrounds (*188*). In a large study of births to U.S. Navy wives, the same complications increased with maternal smoking. In the latter study, the incidence of premature rupture of membranes increased within four levels of maternal smoking from none to 31+ cigarettes per day (*189*). Kullander and Kaellen found a significant increase in the frequency of abruptio placentae among children dying before the age of 1 week (*89*). Andrews and McGarry found increased incidence of abruptio placentae and other forms of accidental antepartum hemorrhage to be associated with maternal smoking. They stated that this was thought to be the cause of premature delivery in 1.2 percent of smokers compared with only 0.5 percent of nonsmokers. The incidence of accidental hemorrhage specific for parity was higher for smokers than for nonsmokers at all parities, rising to 3.16 percent of smokers who were para 4 or more (*2*). Similarly, Russell, et al. found an increase in vaginal bleeding during early pregnancy among women who smoked (*165*). In the study by Goujard, et al., as previously noted, a large proportion of the increase in stillbirths among smokers was caused by abruptio placentae (*63*). Naeye reviewed the clinical and postmortem material from the 3,897 fetal and infant deaths in the Collaborative Perinatal Project of the NINCDS (*137*) and reported an association between perinatal mortality rates caused by abruptio placentae and number of cigarettes smoked by the mother (*131*). Abruptio placentae was the underlying cause identified in 11 percent of all the deaths in this large study (*129*).

The Ontario data corroborated these findings, as shown in Table 11. Increasing levels of smoking resulted in a highly significant increase in the risks of placental abruptions, placenta previa, bleeding, and

TABLE 11.—Perinatal mortality and selected pregnancy complications by maternal smoking levels

Outcome	Smoking level (packs per day) (rates per 1,000 total births)			
	0 (28,358 births)	<1 (15,328 births)	1+ (6,381 births)	Chi square*
Perinatal mortality	23.3	28.0	33.4	27.8†
Abruptio placentae	16.1	20.6	28.9	47.3†
Placenta previa	6.4	8.2	13.1	28.6†
Bleeding during pregnancy	116.5	141.6	180.1	201.9†
Rupture of membranes >48 hours	15.8	23.3	35.8	109.9†
Rupture of membranes only at admission	30.3	39.3	45.0	45.7†

*Cochran's chi square for trends.
†$p<0.00001$.
SOURCE: Meyer, M.B. (*116*).

prolonged rupture of membranes—all of which carry high risks of perinatal loss. Fetal and neonatal deaths from the Ontario study were analyzed (*116*) to look for smoking-related excesses of various complications of pregnancy and labor among those coded by the original Ontario Perinatal Mortality Study (*142*). Results are shown in Table 12. Most diagnoses showed no association with excess mortality for smokers' babies, but a few stood out as highly significant. As shown in Table 10, the net excess of fetal deaths for smoking mothers was 63. Table 12 shows that these deaths were strongly associated with bleeding during pregnancy, either before ($p=0.01$) or after ($p=0.0005$) 20 weeks' gestation, with 88 percent of the total excess falling in these categories. In other coded categories, a significant excess of fetal deaths occurred among smoking mothers with abruptio placentae ($p=0.001$) or other obstetrical problems. Analysis of coded complications of labor showed an excess of 32 fetal deaths coded as abruptio placentae and 8 coded as placenta previa. Fourteen more than expected had prolonged rupture of membranes.

Similar comparisons were made for neonatal deaths (Table 8). For these, the net excess among smoking mothers was 40. Among women who had vaginal bleeding before 20 weeks' gestation, there were 41 more neonatal deaths observed than expected, accounting for the total difference ($p=0.0001$). Other categories that showed significant increases of smoking-associated neonatal deaths are the admission status of rupture of membranes only, other obstetric complications, and duration of rupture of membranes over 48 hours, with 19 more neonatal deaths than expected in the latter group (*116*).

TABLE 12.—Fetal and neonatal deaths by maternal smoking and other coded conditions (Ontario Perinatal Mortality Study data. Canadian-born, English-speaking women, N = 31,789 births, 411 perinatal deaths)

Coded condition	Deaths of smokers' babies Observed-expected differences*			
	Fetal	P†	Neonatal	P†
Admission status				
True labor	15.3	N.S.	26.3	N.S.
Toxemia	-0.9	N.S.	0.7	N.S.
Abruptio placentae	48.5	0.001	2.5	N.S.
Elective cesarean section	-2.3	N.S.	-5.9	N.S.
Induction	-4.9	N.S.	-4.8	N.S.
Rupture of membranes only	0.4	N.S.	13.9	0.04
Other obstetric abnormality	16.8	0.06	6.0	0.01
Duration of rupture of membranes				
< 24 hours	32.2	N.S.	13.7	N.S.
24-48 hours	2.3	N.S.	3.3	N.S.
48+ hours	14.3	N.S.	19.4	0.01
In caul	8.5	0.02	1.7	N.S.
Unknown	5.8	N.S.	1.7	N.S.
Bleeding during pregnancy				
None	2.6	N.S.	-5.4	N.S.
Before 20 weeks	23.7	0.01	41.3	0.0001
After 20 weeks	32.2	0.0005	3.3	N.S.
Complications of labor				
None	19.2	N.S.	22.2	N.S.
Placenta previa	7.6	N.S.	6.6	N.S.
Abruptio placentae	32.3	0.002	6.2	N.S.
Abnormal uterine action	0.7	N.S.	4.9	N.S.
Cephalopelvic disproportion, dystocia	-2.4	N.S.	1.8	N.S.
Tumultuous labor	8.4	N.S.	7.1	N.S.
Postpartum hemorrhage	-4.6	N.S.	-8.0	0.06

N.S. = Not significant.
*Based on nonsmoker rate.
†P value derived from chi square based on a null hypothesis of no difference between smokers and nonsmokers.
SOURCE: Derived from Meyer, M.B. (*116*).

The conclusion may be drawn that maternal smoking increases the risk of fetal and neonatal death at least partly by increasing the incidence of these complications. The mechanisms of action of various components of cigarette smoke in bringing about these events are discussed in another section of this chapter.

Preeclampsia

It has been a consistent finding in almost all published studies that the incidence of preeclampsia and toxemia, however defined, is negatively associated with maternal smoking (*2, 10, 31, 42, 74, 89, 101, 146, 164,*

189, 212). Some of these studies have shown an inverse dose-response relationship, the incidence of preeclampsia declining as the number of cigarettes smoked increased (*146, 189*). Data from the British Perinatal Mortality Study were cross-tabulated by parity, severity of preeclampsia, and maternal smoking status. Smokers had lower rates of all grades of preeclampsia than nonsmokers, whether they were primiparae or multiparae (*20*). Andrews and McGarry showed that the negative relationship between cigarette smoking and preeclamptic toxemia was independent of social class, maternal weight before pregnancy, and maternal weight gain during pregnancy (*2*). Despite the favorable effect of smoking on the incidence of hypertension in pregnancy, there is a greatly increased risk of perinatal mortality if preeclampsia or hypertension does develop in a smoker (*2, 42, 164*). Several authors have suggested that this negative association may be due to the hypotensive effect of thiocyanate, which is derived from the cyanide present in cigarette smoke and regularly found in the blood of smokers (*2, 146*).

Preterm Delivery

Previous sections of this chapter have indicated that the downward shift of the distribution of birth weights with maternal smoking is not accompanied by a similar downward shift of gestational ages. On the other hand, abundant evidence has been presented that a smoking-related increase in preterm delivery plays an important role in the increased risk of neonatal death for the infants of smokers. Explanation of this apparent paradox is found by examination of the distribution by gestational age of births to nonsmokers, light smokers, and heavy smokers as shown in Figure 6, plotted on a semilogarithmic scale to emphasize relative differences in the early weeks. There is little difference between the means of these curves because the great majority of births occur around term in all groups. There is, however, a significant and dose-related increase in the proportions of preterm babies born to women who smoke. These preterm deliveries account for a small proportion of total births but for a large proportion of the deaths (*112*).

Published studies in which the percent of births occurring before term has been related to maternal smoking have consistently shown higher rates for smokers than for nonsmokers. Some examples are shown in Table 13. In four studies where all births and perinatal deaths were included, the risk of early delivery increased from 36 to 47 percent if the mother smoked, and 11 to 14 percent of all preterm births could be attributed to maternal smoking (*2, 20, 47, 207*). The lower relative and attributable risks found in Yerushalmy's study (*207*) may have resulted from selection of particular births to be studied and from the exclusion of fetal deaths. Analysis of the Ontario Study data

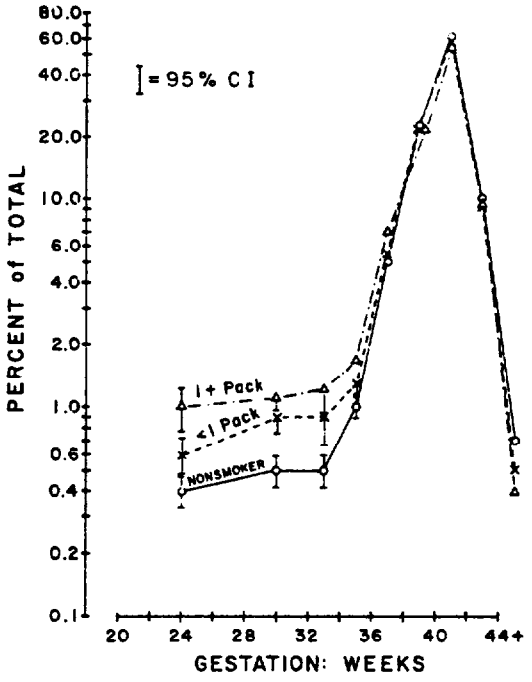

FIGURE 6.—Percentage distribution by weeks of gestation of births to nonsmokers, smokers of less than one pack per day, and smokers of one pack per day or more

SOURCE: Meyer, M.B. (*112*).

showed rates of delivery before 38 weeks of 77 per 1,000 births for nonsmokers, 92 per 1,000 for light smokers, and 116 per 1,000 for heavy smokers, after adjustment for the effects of other maternal factors (*115*).

Pregnancy Complications and Perinatal Mortality by Gestation

Meyer and Tonascia (*116*) have related the excess fetal and neonatal mortality of smokers' infants and the excess incidence of pregnancy complications among women who smoke to the gestational age of occurrence, using a life-table approach. A starting population of all pregnancies *in utero* at 20 weeks was used to calculate the probabilities of fetal death, live delivery followed by survival or death, or the occurrence of a complication followed by fetal death or delivery. At 28 weeks (the next point defined by the data), the population at risk included those remaining *in utero* at that point. Figure 7 shows the risk of perinatal death during each period of gestational age starting at 20 weeks. Risks for smokers' infants were significantly greater in the

TABLE 13.—Preterm births by maternal smoking habit, relative and attributable risks, derived from published studies

Study	Smokers (proportion)	Preterm births* per 100 total births		Relative risk: Smokers/Non-smokers	Attributable risk** %
		Nonsmokers	Smokers		
Cardiff (2)	.465	6.7	9.2	1.36	14
Great Britain (20)	.274	4.7	6.9	1.47	11
Montreal (47)	.432	7.7	10.6	1.38	14
Ontario***	.435	7.4	10.1	1.36	4
California (207)					
White	.402	5.9	6.9	1.10	4
Black	.338	13.4	16.7	1.25	8

*Cardiff and Ontario data are for < 38 weeks. All others are for < 37 weeks.
**Failure of totals to agree is due to omission of unknowns.
***Unpublished, derived from original data.

earlier weeks, remaining higher until term. Separate calculations for fetal and neonatal deaths (not shown) indicated a fetal death pattern very similar to the one shown for perinatal deaths. Neonatal deaths appeared to be due solely to an increased risk of early delivery among smokers' babies, rather than to differences in survival between smokers' and nonsmokers' babies of the same gestational age.

A similar approach was applied to the risk of abruptio placentae, placenta previa, and premature rupture of membranes for smokers and nonsmokers, as shown in Figure 8. All of these complications are more frequent in smokers than in nonsmokers throughout gestation, but again the biggest differences occur in the weeks of pregnancy from 20 to 32 or 34 weeks (*116*). The relationships between maternal smoking, these complications, early fetal death, and preterm delivery accompanied by neonatal death are apparent from the statistical associations between them and from the similar time patterns they share.

Sudden Infant Death Syndrome

Maternal smoking habits have been ascertained in several studies of the sudden infant death syndrome (SIDS). In all of these, a positive association has been found between maternal smoking during pregnancy and the incidence of sudden infant death. Steele and Langworth, in a study of 80 cases, each with two matched controls, which were traced back to the Ontario Perinatal Mortality Study population of 1960-61, found that sudden infant deaths were strongly associated with the frequency of maternal smoking during pregnancy ($p<0.001$) and also with the level of maternal smoking. Thirty-nine percent of the cases were nonsmokers versus 60 percent of controls; 36 percent of the

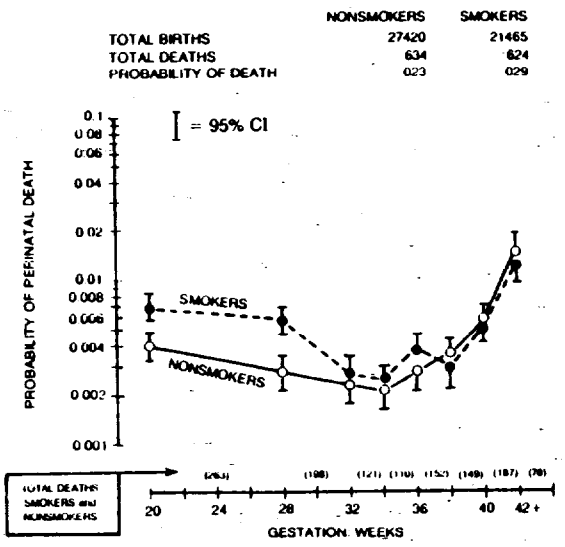

FIGURE 7.—Probability of perinatal death for smoking and nonsmoking mothers, by period of gestational age. Bars show 95 percent confidence intervals

SOURCE: Meyer, M.B. (*116*).

cases and 27 percent of the controls smoked less than a pack per day; 24 percent of the cases and 10 percent of the controls smoked a pack per day or more. The habits of the remaining 1 to 2 percent of mothers were unknown (*180*). Bergman and Wiesner noted the effects of exposure to cigarette smoke (passive smoking) on infants, including the increased frequency of respiratory infections in the infants of smoking mothers, and stated their impression that the amount of smoking seemed unusually heavy at meetings of parents who had lost children to SIDS. The authors studied 56 families who lost babies to the sudden infant death syndrome and 86 control families. They reported that a higher proportion of SIDS mothers smoked during pregnancy than controls (61 percent versus 42 percent), more smoked after pregnancy (59 percent versus 42 percent), and SIDS mothers smoked a significantly greater number of cigarettes than controls. These authors indicate that exposure to cigarette smoke (passive smoking) appears to enhance the risk for SIDS for reasons not yet known (*15*). However, whether prenatal or postnatal exposure is more important cannot be determined. Naeye, et al., in their analysis of 125 SIDS victims from the population of the Collaborative Perinatal Project of the NINCDS, stated: "The gestations that produced the SIDS victims were characterized by a greater frequency of mothers who smoked cigarettes and had anemia" than was true for the whole population of 53,721 infants or for a set of 375 controls matched on important factors

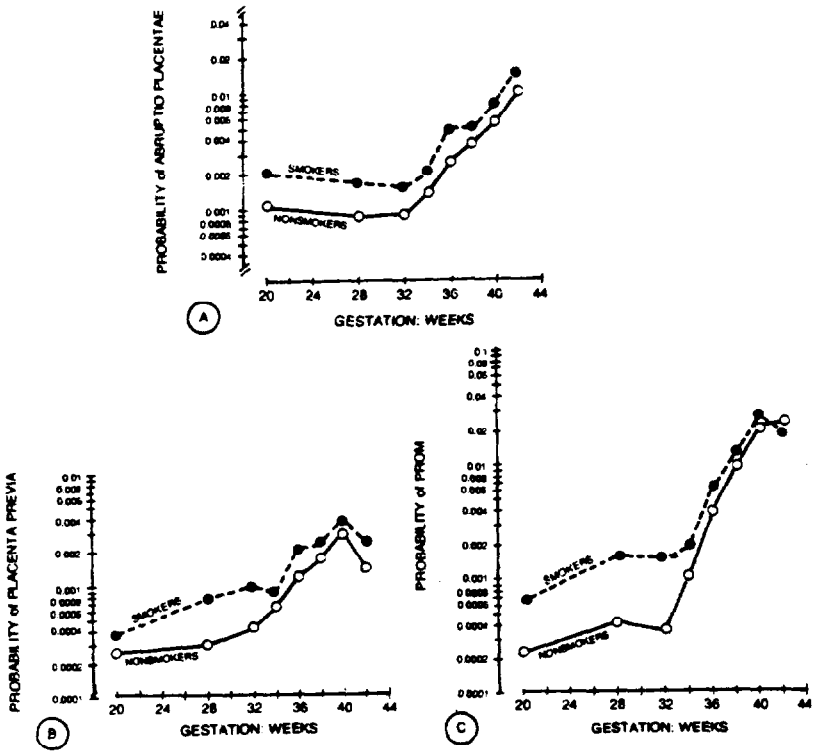

FIGURE 8.—Risks of selected pregnancy complications for smoking and nonsmoking mothers, by period of gestational age at delivery. A—abruptio placentae; B—placenta previa; C—admission diagnosis, rupture of membranes only

SOURCE: Meyer, M.B. (*116*).

(*130*). Rhead, commenting on studies published to date which demonstrate an increased incidence of maternal cigarette smoking in SIDS, states: "It is now...clear that maternal cigarette smoking contributes to an infant's risk of dying from SIDS" (*159*).

Summary

1. The risk of spontaneous abortion, of fetal death, and of neonatal death increases directly with increasing levels of maternal smoking during pregnancy.

2. Published studies of smoking during pregnancy show a range of perinatal mortality risk ratios (smokers versus nonsmokers) from a low of 1.01 to a high of 2.42.

3. Causes of variability between risk ratios in different study populations have been explained by recent analyses. They include:

(a) Lack of comparability between smokers and nonsmokers with respect to other important variables that influence perinatal mortality, such as race, socioeconomic status, age, parity, and others.

(b) Interaction between the effects of maternal smoking and these other variables, which makes maternal smoking more dangerous for the fetus in some pregnancies than in others.

4. Studies failing to take account of these other variables may show unusually high or unusually low risk ratios.

5. In one large study, the perinatal mortality risk increased by 20 percent for the infants of smokers of less than a pack per day and by 35 percent for smokers of a pack per day or more, compared with nonsmokers, after simultaneous adjustment to balance the effects of variables other than smoking. These increases are similar to those of other large studies with appropriate control of other variables.

6. Excess deaths of smokers' infants are found mainly in the coded cause categories of "unknown" and "anoxia" for fetal deaths, and in the categories of "prematurity alone" and "respiratory difficulty" for neonatal deaths. This finding indicates that the excess deaths result not from abnormalities of the fetus or neonate, but from problems related to the pregnancy.

7. Increasing levels of maternal smoking result in a highly significant increase in the risks of placental abruptions, placenta previa, bleeding early or late in pregnancy, premature and prolonged rupture of membranes, and preterm delivery—all of which carry high risks of perinatal loss.

8. Although there is little effect of maternal smoking on mean gestation, the proportion of fetal deaths and live births that occur before term increases directly with maternal smoking level. Up to 14 percent of all preterm deliveries in the United States may be attributable to maternal smoking.

9. According to the results of one large study, the most significant difference between smokers' and nonsmokers' risk of perinatal mortality and pregnancy complications occurs at the gestational ages from 20 weeks to 32 or 36 weeks.

10. These findings lead to the conclusion that maternal smoking can be a direct cause of fetal or neonatal death in an otherwise normal infant. The immediate cause of most smoking-related fetal deaths is probably anoxia, which can be attributed to placental complications with antepartum bleeding in 30 percent or more of the cases. In other cases, the oxygen supply may simply fail from reduced carrying capacity and reduced unloading pressures for oxygen caused by the presence of carbon monoxide in maternal and fetal blood. Neonatal deaths occur as a result of the increased risk of early delivery among smokers, which may be secondarily related to bleeding early in pregnancy and premature rupture of membranes.

Lactation and Breast Feeding

Introduction

In 1902, Ballantyne (*9*) suggested the possibility of detrimental effects of breast feeding on babies whose mothers worked in tobacco factories. In the intervening years, questions have been raised concerning the interaction between cigarette smoking and lactation, as well as the relationship of cigarette smoking to the quantity of milk produced, to the presence of constituents of cigarette smoke within the milk, and to effects upon the nursing infant mediated through changes in either the quantity of milk available or the substances within the milk.

Epidemiological Studies

Underwood, et al. (*188*), in a study of 2,000 women from various social and economic strata, observed a trend, though statistically insignificant, toward more frequent inadequacy of breast milk production among those smoking mothers who attempted to nurse, as compared to nonsmokers. They concluded that smoking does not interfere with breast feeding to any significant degree. However, this study, based on interviews of puerperal women, was not designed to analyze the effect of smoking on breast feeding and presents only percentile results. No data are provided to permit a reanalysis to determine the validity of their conclusions.

Perlman, et al. (*149*) also present anecdotal data. They found that in their postpartum population practically all smoking women started to consume cigarettes within two days after delivery. Although they collected milk between the fourth and ninth postpartum days to determine nicotine content, they do not report and compare actual amounts of milk secreted by both smokers and nonsmokers. They noted that of the 55 smoking, lactating mothers, 11 failed to have enough breast milk for the needs of their babies. No comparative study was done in a nonsmoking but otherwise equivalent population.

Mills (*120*) studied the nursing patterns of 520 women giving birth to their first live-born infant. Among the mothers nursing their babies for a minimum of 2 months and beyond, the mean nursing period was significantly shorter for smokers than for nonsmokers. Moreover, among the 24 mothers who had given up smoking during at least the final 3 months of their pregnancies, the average length of nursing was identical to that of the nonsmokers. There was no significant difference between smokers and nonsmokers with regard to complete inability to nurse their offspring. This study is difficult to interpret because the author did not determine the reason(s) for the discontinuation of nursing among the women.

Surveys of larger populations of women, smokers and nonsmokers, are needed to determine accurately the effect of smoking on milk