pared with never smokers. All former smokers had a 1.6-fold increase, but this increase was limited to those who had quit within the preceding 8 years. Longer durations of abstinence yielded an odds ratio of 1.0.

Concerns about the possibility of differences in sexual activity between smokers and nonsmokers and the occurrence of STDs limit the ability to draw firm conclusions about the association of smoking with ectopic pregnancy. There is little information about former smokers, and consequently, no conclusion can be drawn.

Some data suggest an association between smoking and increased risk of spontaneous abortion (US DHHS 1989). Data on smoking cessation are very sparse. Kline (1984) noted that the adverse effect of smoking observed in a case–control study of smoking and spontaneous abortion (Kline et al. 1977) was limited to current, not former, smokers. Alberman and colleagues (1976) found that the proportion of spontaneous abortions with abnormal karyotypes decreased with increased smoking but was identical for never smokers and women who stopped smoking prior to pregnancy (Alberman et al. 1976). The interpretation of this finding is uncertain.

Fetal, Neonatal, and Perinatal Mortality

Information linking cigarette smoking with an increased risk of the various measures of mortality used to assess pregnancy outcome has been reviewed in previous reports of the Surgeon General and other publications (US DHEW 1979; US DHHS 1980; US DHHS 1986). Table 3 provides data on perinatal and neonatal mortality from the earlier reports of the Surgeon General (US DHEW 1979; US DHHS 1980) and adds information from a more recent publication on the topic (Rush and Cassano 1983). The studies are consistent in indicating higher mortality in children born to women who smoke. The high risk of mortality is independent of various factors, such as education and social class, that are also associated with mortality.

Kleinman and colleagues (1988) assessed the effect of smoking on fetal and infant mortality in 362,621 births in Missouri during 1979–1983. Using multivariate statistical techniques, these investigators estimated the effects of smoking on fetal and infant mortality among black and white primiparous and multiparous women. After adjustment for marital status, education, and age, fetal plus infant mortality rates were 25 to 56 percent higher in smokers for all categories of maternal race and parity. The elevations in the estimated risks of fetal plus infant mortality were statistically significant in all categories. In further analyses of data from the Missouri births and deaths, Malloy and coworkers (1988) showed that the relative risk of fetal plus infant mortality among whites was significantly elevated for the infants of women who smoked in all categories of low birthweight, even after adjustment for marital status, education, age, and parity (Table 4). This data set is unique in its size, consisting of more than 350,000 births. The data indicate that even in the normal birthweight infants of smokers—those that weighed 2,500 g or more—mortality was significantly elevated for infants of mothers who smoked.

Information on fetal, neonatal, and perinatal mortality in former smokers is sparse (Table 5). Butler, Goldstein, and Ross (1972) analyzed data from the British Perinatal Mortality Survey and estimated that perinatal mortality was the same for women who

TABLE 3.—Summary of studies of perinatal and neonatal mortality in smokers and nonsmokers during pregnancy

Reference	Number of births	Category	Perinatal mortality[a]		Neonatal mortality[a]	
			Smokers	Nonsmokers	Smokers	Nonsmokers
Yerushalmy (1964)	6,800	Whites			13.9	12.4
		Blacks			22.0	23.4
Comstock and Lundin (1967)	12,287				23.6[b]	15.6[b]
		Amount smoked				
Meyer and Tonascia (1977)	51,490	<1 ppd	28.0	23.0		
		≥1 ppd	33.4			
		Social class[c]				
Rantakallio (1978)	12,068	I+II	28.1[d]	22.4[d]		
		III+IV	25.1	19.6		
		Farmers	25.5[d]	39.0[d]		
		Unknown	29.4[d]	36.8[d]		
		Amount smoked				
Rush and Cassano (1983)		<5 cig/day	15.9	18.7		
		5–14 cig/day	26.1			
		>15 cig/day	28.3			
Butler, Goldstein, Ross 1972)	21,788		41.1	32.0	17.6	13.7
		Amount smoked				
Andrews and McGarry (1972)	18,631	1–4 cig/day	25	24		
		5–9 cig/day	20			
		10–19 cig/day	32			
		≥20 cig/day	36			
		Race and Amount smoked				
Niswander and Gordon (1972)	37,912	White		31.4		
		1–10 cig/day	31.5			
		≥11 cig/day	38.2			
		Black		38.5		
		1–10 cig/day	41.5			
		≥11 cig/day	57.4			

TABLE 3.—Continued

Reference	Number of births	Category	Perinatal mortality[a]		Neonatal mortality[a]	
			Smokers	Nonsmokers	Smokers	Nonsmokers
		Race				
Rush and Kass (1972)	3,266	White	31.4	29.2		
		Black	54.1	28.6		
		Maternal age				
Fabia (1973)	6,879	<25 yr	16.1	12.1		
		25–34 yr	13.2	12.6		
		≥35 yr	41.7	23.0		

NOTE: ppd= packs/day.
[a]Per 1,000; definition of mortality as in paper cited.
[b]Adjusted for sex of infant and father's education.
[c]Defined in paper cited.
[d]Rate based on five deaths or fewer.

TABLE 4.—Estimated relative risk of fetal plus infant mortality for maternal smoking in several birthweight groups, adjusting for maternal marital status, education, age, and parity

Birthweight group (g)	Estimated relative risk	95% CI
500–999	1.71	1.46–2.00
1,000–1,499	1.78	1.58–2.01
1,500–1,999	2.00	1.84–2.18
2,000–2,499	2.44	2.33–2.55
≥2,500	1.24	1.10–1.39

NOTE: Figures are for whites only. CI=confidence interval.
SOURCE: Malloy et al. (1988).

smoked prior to conception and who stopped before the fourth month of pregnancy as it was for never smokers. However, perinatal mortality was higher for continuing smokers than for never smokers for all categories of amount smoked. Andrews and McGarry (1972) examined mortality in the Cardiff birth survey of more than 18,631 births. Perinatal mortality was 29 per 1,000 in those who quit smoking before pregnancy or in the early months of pregnancy; 29 per 1,000 in continuing smokers; and 24 per 1,000 in "nonsmokers." Rush and Cassano (1983) analyzed data from the 1970 British birth cohort, consisting of all births in Great Britain during a single week in 1970.

Perinatal mortality among those who smoked before pregnancy but quit during pregnancy (15.0/1,000) was lower than for either nonsmokers during pregnancy (18.7/1,000) or smokers of 5 cigarettes or more per day throughout pregnancy (26.9/1,000).

TABLE 5.—Summary of studies of perinatal mortality in smokers throughout pregnancy, smokers who quit in the early months of pregnancy, and nonsmokers during pregnancy

Reference	Number of births	Perinatal mortality[a]				
		Nonsmokers	Former smokers		Smoked throughout pregnancy	
Butler, Goldstein, Ross (1972)	21,788	32.2	1–4 cig/day	31.7[b]	1–4 cig/day	38.5
			5–9 cig/day	31.1	5–9 cig/day	42.2
			10–19 cig/day	28.1	10–19 cig/day	41.6
			20–30 cig/day	35.2	20–30 cig/day	41.2
Andrews and McGarry (1972)	18,631	24		29[c]		29
Rush and Cassano (1983)	16,688	18.7		15.0[d]		26.9

[a]Late fetal and neonatal deaths/total births × 1,000.

[b]Women who quit smoking before the fourth month of pregnancy.

[c]Women who quit smoking before pregnancy or during early pregnancy.

[d]Women who quit smoking during early pregnancy.

Fetal, neonatal, and perinatal mortality are rare events. This limits the study of their association with smoking cessation. Lack of data makes it impossible to draw a firm conclusion about the association of smoking cessation with the risk of fetal, neonatal, or perinatal mortality. However, the limited available data are consistent with the conclusion that perinatal and neonatal mortality are lower among infants of women who quit smoking than among those women who smoke throughout pregnancy. The possibility must be considered that differences between women who quit smoking and those who continue to smoke account for the lower rate of perinatal and neonatal mortality in the studies in which this has been observed.

Birthweight and Gestational Duration

Introduction

Fetal, neonatal, and perinatal mortality are the most direct measures of pregnancy outcome. Mortality is relatively uncommon, and very large samples are needed for study. This has led to the widespread study of birthweight and the percentage of births that are low birthweight (<2,500 g) as surrogates for the study of mortality. This strategy has been justified by the extremely strong association between birthweight and the percent of low birthweight and each of the measures of mortality (Figure 1). Equally important is weight at birth as a determinant of infant health (McCormick 1985).

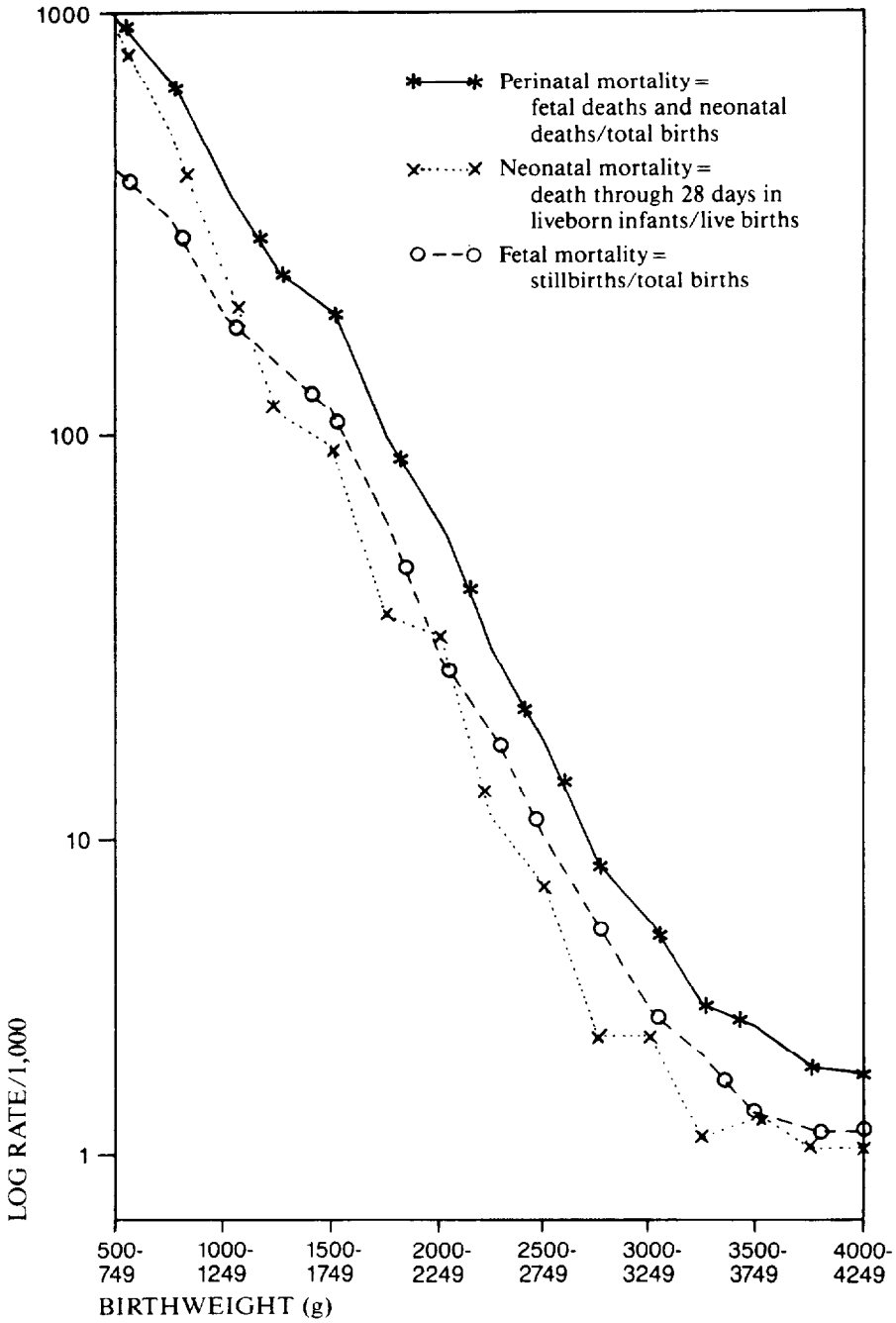

FIGURE 1.—Perinatal, neonatal, and fetal mortality rates by birthweight in singleton white males, 1980

SOURCE: Williams and Chen (1982).

Birthweight is, however, a result of gestational age at birth and the rate of fetal growth. Recognition of the complex relationships among gestational duration, rate of fetal growth, birthweight, and mortality has led to attempts to classify infants according to gestational duration or joint distribution of birthweight and gestational duration. Generally, births are categorized as preterm (<37 weeks gestation) and/or as small for gestational age (SGA) (<10th percentile of weight for a given gestational age). Joint classification is thought to provide a more discriminating basis for the study of etiologic agents.

Preterm delivery is strongly associated with increases in the risk of fetal, neonatal, and perinatal mortality and with significant childhood morbidity. Both preterm delivery and SGA increase the risk of cerebral palsy, although the risk is much greater for preterm delivery (Ellenberg and Nelson 1979). SGA is associated with increased risk of neonatal and perinatal mortality at every gestational age (Koops, Morgan, Battaglia 1982; Lubchenco, Searls, Brazie 1972); with SIDS (Buck et al. 1989); and with neurocognitive deficits, short stature, and small head circumference in childhood (Fitzhardinge and Steven 1972; Hill et al. 1984; Westwood et al. 1983; Ounsted and Taylor 1971; Harvey et al. 1982; Ounsted, Moar, Scott 1984, 1988; Fancourt et al. 1976).

Continued Smoking

As reviewed in previous Surgeon General's reports (US DHEW 1979; US DHHS 1980) and in other literature (Landesman-Dwyer and Emanuel 1979; Longo 1982; Werler, Pober, Holmes 1985; Kramer 1987), smoking during pregnancy decreases mean birthweight and increases the proportion of low birthweight births. Estimates vary among studies, but birthweight is reduced by an average of approximately 200 g, and the proportion of low birthweight is approximately doubled by cigarette smoking (Meyer, Jonas, Tonascia 1976; US DHHS 1980; US DHEW 1979; McIntosh 1984; Committee to Study the Prevention of Low Birthweight 1985; Kramer 1987). Mean birthweight decreases and the percent low birthweight increases with increasing number of cigarettes smoked daily. The relationship between cigarette smoking and decreased birthweight is considered to be causal (US DHEW 1979; US DHHS 1980, 1989).

Smoking affects birthweight and the percentage of babies who are born of low birthweight by retarding fetal growth. A measure of fetal growth retardation is the probability of delivering an infant who is in the less than 10th percentile for gestational age. The relative risk of SGA is about 3.5- to 4.0-fold higher among the infants of smokers than for the infants of nonsmokers (Ounsted, Moar, Scott 1985). Preterm birth is also associated with maternal smoking, although not as strongly. Estimates of the relative risk of delivering before 37 weeks of gestation are typically about 1.5 for smoking during pregnancy (Committee to Study the Prevention of Low Birthweight 1985; Kramer 1987; Shiono, Klebanoff, Rhoads 1986). Mean gestational duration among smokers is not significantly shorter than it is among nonsmokers (US DHEW 1979; US DHHS 1980). This finding is consistent with the observation that the risk of delivering early is greater among smokers than nonsmokers, but the percentage of

preterm deliveries is so small that the mean would not be affected unless the shift were very large (US DHEW 1979; US DHHS 1980).

Cessation Before Conception

Most studies of cigarette smoking and birthweight have failed to separate never smokers from women who quit smoking prior to conception. MacMahon, Alpert, and Salber (1966) first examined the association of pre-pregnancy smoking with birthweight and found no significant difference in the mean birthweight of infants whose mothers smoked before but not during pregnancy compared with never smokers. Subsequent research has confirmed the absence of an association between smoking prior to conception and reduced birthweight (Table 6). In all of these studies, smokers who quit before conception had mean birthweight values that were equivalent or higher than those of never smokers. Other studies in which information on mean birthweight could not be derived (Kline, Stein, Hutzler 1987; Anderson et al. 1984; Wainright 1983), with the exception of Zabriskie (1963), have also consistently shown no association between birthweight and smoking that ceased prior to conception. Zabriskie (1963) failed, however, to adjust for smoking during pregnancy, and these results are not directly pertinent in a comparison of birthweight in never smokers and smokers who quit before conception.

TABLE 6.—Summary of studies of mean birthweight, by smoking status

Reference	Mean birthweight (g)		
	Never smoked	Smoked before but not during pregnancy	Smoked during pregnancy
Cope, Lancaster, Stevens (1973)	3,376	3,395	3,200
Van den Berg (1977)	3,463	3,457	3,255
Rush and Cassano (1983)	3,357	3,384	NR
Višnjevac and Mikov (1986)	3,327	3,331	3,097

NOTE: NR=not reported.

In interpreting these data, misclassification of exposure needs to be considered. MacArthur and Knox (1988) reported that women who quit smoking during pregnancy, and possibly those who quit before pregnancy, were more often living with a partner who smoked. Passive smoke exposure may adversely affect the fetus (Martin and

Bracken 1986). Furthermore, for whatever reason, some women may misrepresent their smoking status, denying that they have continued smoking, thus leading to an underestimation of the benefit of smoking cessation prior to conception.

More important, women who quit smoking prior to conception differ in other respects from women who continue to smoke. Women who quit may have smoked fewer cigarettes per day prior to quitting. Studies of smoking cessation prior to conception have not accounted fully for other differences between women who quit and those who continue to smoke.

Cessation After Conception

Birthweight

Table 7 summarizes nonexperimental studies in which information on mean birthweight in nonsmokers, smokers throughout pregnancy, and smokers who quit after conception could be derived. The data from each of these studies are consistent in two important ways. First, women who smoked throughout pregnancy delivered infants who weighed less than the infants of nonsmokers. Second, women who quit smoking delivered infants who weighed more than the infants of smokers throughout pregnancy. In most of these studies, mean birthweight values among infants whose mothers stopped smoking were the same or higher than those of infants of nonsmokers.

Table 8 summarizes nonexperimental studies estimating the relative risk of low birthweight for continuing smokers and quitters some time during pregnancy compared with nonsmokers during pregnancy. These studies are consistent with those examining mean birthweight. Compared with nonsmokers, the risk of low birthweight is elevated among smokers throughout pregnancy, and the risk is about 1.0 for women who quit. In addition, Kleinman and Madans (1985) reported no association between the risk of low birthweight for women who quit smoking during pregnancy compared with those who had not smoked in the 12 months prior to conception among participants in the 1980 National Natality Survey (NNS).

An important aspect of smoking cessation and pregnancy outcome is the timing of cessation during pregnancy and its relation to birthweight. How early in pregnancy cessation must occur to avoid the adverse effects of smoking on birthweight is a key issue with important implications for counseling pregnant smokers.

In most of the studies examining this question, only information on cessation in the early months of pregnancy is presented. However, Rush and Cassano (1983) found that mean birthweight among women who quit as late as the seventh to eighth month of pregnancy was higher than for women who smoked throughout pregnancy, but lower than for nonsmokers and for women who quit earlier in gestation. MacArthur and Knox (1988) concluded that quitting any time before the 30th week of gestation increases birthweight when compared with continuing to smoke. Cooper (1989) assessed patterns of cigarette smoking by trimester of pregnancy. Women who reported smoking during the "first trimester of pregnancy only" had a 30-percent increased risk of having a low birthweight baby, while women who reported smoking during the "first and second trimester of pregnancy only" had a 70-percent higher risk of a low

TABLE 7.—Summary of nonexperimental studies of smoking cessation after conception, mean increase (+) or decrease (–) in birthweight (g) according to timing of cessation

Reference	Month of cessation									Unknown	Smoked throughout
	1	2	3	4	5	6	7	8	9		
Lowe (1959)					+14						–182
Underwood et al. (1967)			–108			–152					–230
Butler, Goldstein, Ross (1972)				+46							–160
Andrews and McGarry (1972)			–80								–170
Papoz et al. (1982)						+10					–70
Rush and Cassano (1983)	+98					+43		+36	–90		–155
Pulkkinen (1985)			–61								–225
Counsilman and MacKay (1985)			–40								–235
Kline, Stein, Hutzler (1987)										+12	–202
MacArthur and Knox (1988)	+22			–58							–242

NOTE: Mean increases or decreases are relative to nonsmokers during pregnancy.

birthweight baby. Women who reported smoking throughout their pregnancy had a 90-percent increased risk of having a low birthweight baby in contrast to nonsmokers.

Most fetal growth occurs late in pregnancy, and the primary smoke constituents considered as candidates in mediating the effect of smoking on fetal growth (i.e., CO and nicotine leading to intrauterine hypoxia) have short-term reversible effects. The data in Tables 6 and 7 support the conclusion that the adverse effect of smoking on birthweight occurs in the latter part of gestation, primarily during the third trimester, and that cessation at any time during gestation is likely to mitigate the adverse effect of smoking on fetal growth.

Because it is difficult to persuade all pregnant smokers to quit smoking entirely, the benefit of reducing the number of cigarettes smoked per day becomes a public health issue. The observation that cigarette smoking retards fetal growth in a dose–response

TABLE 8.—Summary of nonexperimental studies of relative risk of low birthweight for smoking cessation after conception

Reference		Relative risk[a]	
		Ceased smoking after conception	Smoked throughout pregnancy
Frazier et al. (1961)		1.0	1.7
Van den Berg (1977)[b]		1.6	3.0
Petitti and Coleman (in press)			
Whites	<1 mo	0.5	2.7
	1–2 mo	1.0	
	2–3 mo	0.6	
Blacks	<1 mo	1.4	3.8
	1–2 mo	1.0	
	2–3 mo	1.1	
Andrews and McGarry (1972)		1.3	2.0

[a]Compared with nonsmokers during pregnancy.

[b]Whites only.

fashion supports the benefit of reducing the number of cigarettes smoked per day. Hebel, Fox, and Sexton (1988) used data from their randomized trial of smoking cessation to examine this question. These researchers found that the benefit of decreased smoking for birthweight during pregnancy was almost entirely restricted to those who achieved total cessation, perhaps because women who reduce the number of cigarettes smoked compensate by inhaling more deeply, by puffing more frequently, or by smoking the cigarette to a shorter butt length. Findings from another randomized trial support the conclusion that abstinence, not reduction, should be the goal in pregnancy (MacArthur, Newton, Knox 1987). In this latter study, the intervention led to a considerable reduction in the reported mean number of cigarettes smoked per day but almost no difference in the percentage of women who quit entirely; there was no difference in birthweight between the treatment and control groups (MacArthur, Newton, Knox 1987). Because of the social stigma associated with smoking during pregnancy, it is possible that some women in this intervention trial falsely reported a reduction in smoking; if so, this underreporting would lead to an underestimation of possible benefits of reducing cigarette consumption.

Whether quitting only during the first half of pregnancy will prevent a reduction in birthweight is another important consideration. Most fetal growth takes place in the last trimester; early quitting virtually eliminates the effect of smoking on birthweight. Thus, smoking late in pregnancy may have an adverse effect on birthweight even if there is abstinence in the first trimester. Lowe (1959) found that the mean birthweight of infants of smokers who quit early in pregnancy but resumed smoking was between that of smokers throughout pregnancy and that of never smokers. Infants of women who gave up cigarettes by the fifth month of pregnancy and who did not resume smoking

had a mean birthweight identical to that of never smokers. MacArthur and Knox (1988) also found that infants born to women who quit smoking early in their pregnancy but started again before delivery had a mean birthweight value between that of smokers throughout pregnancy and those of both early quitters and never smokers. These data indicate that abstinence throughout the third trimester of pregnancy is necessary to realize the full benefit of smoking cessation for birthweight.

Preterm Delivery

The effect of smoking on birthweight is principally due to a reduction in size for a given gestational age rather than to a large decrease in gestational duration (US DHEW 1979; US DHHS 1980). Thus, it would be expected that pregnancy outcome in women who quit would reflect a predominant effect on size for gestational age.

Andrews and McGarry (1972) considered preterm delivery as a distinct endpoint in continuing smokers and quitters; the latter group included a mixture of women who quit prior to conception and women who quit during their pregnancy. The rate of preterm delivery among nonsmokers was 6.7 per 100 compared with 7.5 per 100 for ex-smokers and 9.2 per 100 for women who continued to smoke throughout pregnancy (Andrews and McGarry 1972).

Berkowitz, Holford, and Berkowitz (1982) examined the association between smoking during each trimester of pregnancy and the risk of preterm delivery in a case–control study of 175 mothers of singleton, preterm infants and 313 mothers of singleton, term infants. The risk of preterm delivery was increased among women who smoked in the third trimester of pregnancy, especially if they smoked heavily (>10 cigarettes per day).

Using data from a longitudinal study of pregnant women, Van den Berg and Oechsli (1984) reported rates of preterm delivery (≤37 weeks) among never smokers, smokers who stopped at the beginning of pregnancy, and continuing smokers for 10,947 white women whose singleton pregnancies progressed beyond 22 weeks. The rate of preterm delivery was 5.4 percent in never smokers, 6.8 percent in quitters, and 7.6 percent in continuing smokers. The difference in the rate of preterm delivery between never smokers and quitters was not statistically significant ($p>0.05$); however, the difference between never smokers and continuing smokers was significant.

In a population-based case–control study of white and black women delivering singleton infants without congenital anomalies in a large urban county, Petitti and Coleman (in press) reported that the estimated relative risk of very low birthweight (<1,500 g) or of other preterm births among black and white women who quit smoking prior to the fourth month of gestation was not increased in comparison with those of nonsmokers. The estimated relative risk of very low birthweight (<1,500 g) in continuing smokers was 2.5 for whites and 3.1 for blacks and that of other preterm births was 2.0 for whites and 3.7 for blacks.

MacArthur and Knox (1988) examined gestational duration according to smoking during pregnancy. Mean gestational length was 1.7 days shorter among continuing smokers than nonsmokers. Compared with nonsmokers, gestational periods were 0.4 days shorter for women who quit smoking by the 6th week of pregnancy, 1.5 days longer

for women who quit between the 6th and 16th weeks of pregnancy, and 0.3 days longer for women who quit after the 16th week of pregnancy.

Because of the limited data on the risk of preterm delivery among women who quit smoking after conception, a firm conclusion about benefit, or lack of benefit, attributable to smoking cessation for this pregnancy outcome cannot be drawn.

Complications of Pregnancy

Women who smoke during pregnancy are at increased risk of bleeding during pregnancy and of placenta previa and abruptio placentae (US DHEW 1979; US DHHS 1980; Naeye 1978; Naeye 1980). These women are probably at decreased risk of preeclampsia (US DHEW 1979; US DHHS 1980; Marcoux, Brisson, Fabia 1989). Few data on these pregnancy complications among former smokers are available.

In Naeye's (1980) analysis of data from the Collaborative Perinatal Project, smoking for more than 6 years (but not short-term smoking) was found to be associated with a relative risk of 1.6 to 1.9 for abruptio placentae and a relative risk of 2.4 to 2.8 for placenta previa. Women who had stopped smoking by their first prenatal visit were not at increased risk of abruptio placentae, but were still at twofold increased risk of placenta previa if they were long-term smokers. However, the latter result was based on only 18 exposed cases.

Marcoux, Brisson, and Fabia (1989) found that, compared with women who had never smoked, those who smoked at the time of conception were protected from preeclampsia (estimated relative risk (RR)=0.51), whereas women who smoked but quit prior to conception had the same risk of preeclampsia as never smokers (RR=0.97). Women who smoked at conception but quit prior to 20 weeks' gestation were not as protected from development of preeclampsia as were continuing smokers. Because of the otherwise serious adverse effects of smoking on the fetus, this minor "benefit" of smoking during pregnancy probably has no public health consequence.

Randomized Trials of Smoking Cessation During Pregnancy

Three randomized trials have been conducted on pregnancy outcome in relation to advice to stop smoking (Donovan 1977; Sexton and Hebel 1984; MacArthur, Newton, Knox 1987). Table 9 summarizes the studies and birthweight results. Two other randomized trials have also been conducted on the effect of various programs on smoking cessation rates among pregnant women (Ershoff, Mullen, Quinn 1989; Windsor et al. 1985), and other trials are in progress. Information on pregnancy outcome is not available, and these studies are not reviewed.

Donovan (1977) studied smokers in three maternity units in England. Women aged 35 years or younger at the start of pregnancy, who smoked more than 5 cigarettes per day, who had less than 30 weeks of gestation at the first prenatal visit, and who had no prior perinatal deaths, were randomly assigned to a control group that received usual prenatal care or to a test group that was given intense individual antismoking advice by a physician at each prenatal care unit. There were 263 women in the test group and 289 in the control group. Mean daily cigarette consumption decreased from 17.1 cigarettes per day early in pregnancy to 9.2 cigarettes per day late in pregnancy in the intervention

for women who quit between the 6th and 16th weeks of pregnancy, and 0.3 days longer for women who quit after the 16th week of pregnancy.

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TABLE 9.—Summary of birthweight outcome in randomized trials of smoking cessation in pregnancy

Reference	Number of subjects		Smoking at end of pregnancy		Birthweight (g)		
	I	C	I	C	I	C	Difference (g)[a]
Donovan (1977)	263	289	9.2 cig/day	16.4 cig/day	3,172	3,184	−12
Sexton and Hebel (1984)	463	472	57.0%	80.0%	3,278	3,186	+92
MacArthur, Newton, Knox (1987)	493	489	91%	94%	3,164	3,130	+34

NOTE: I=intervention group; C=control group.

[a]Mean in intervention minus mean in control.

group, but increased slightly from 14.7 to 16.4 in the control group. Mean birthweight was 3,172 g in the test group and 3,184 g in the control group. In the test group 10 percent of the infants had low birthweight (<2,500 g) compared with 9 percent in the control group. There were four perinatal deaths in the test group and one in the control group. None of the differences in birth outcome between the test and control groups were statistically significant.

Although this trial might be regarded as evidence against a benefit of smoking cessation during pregnancy, a number of limitations of the study must be considered. First, no data are presented concerning the percentage of pregnant smokers who quit smoking entirely. Reducing cigarette consumption almost certainly has a smaller benefit for pregnancy outcome than complete cessation. Second, the time at which smoking behavior changed during pregnancy is unclear; data on cigarette consumption for three periods during pregnancy were obtained postnatally, and may have been affected by recall bias. Data from observational studies discussed in the previous section strongly suggest that smoking during the last trimester of pregnancy is a critical mediator of reduction in fetal growth among smokers.

Information from another British randomized trial (MacArthur, Newton, Knox 1987) also questions the benefit of smoking cessation during pregnancy. In this study, women who smoked at the time they were scheduled for a prenatal visit at a large hospital were assigned randomly to a control group that received routine care or to an intervention group that received supplementary health education about smoking during pregnancy. The planned intervention consisted of advice to stop smoking and information about the effects of smoking on the fetus, presented visually by a booklet or verbally by the obstetrician. There were 489 women in the control group and 493 in the intervention group. Mean birthweight for infants in the control group was 3,130 g compared with 3,164 g for the intervention group. The percentages of low birthweight and perinatal mortality in the two groups were not reported. The difference in mean birthweight was

not statistically significant as determined by the conventional 0.05 probability value and a two-sided test.

In this trial, only 9 percent of the women in the intervention group quit smoking entirely, compared with 6 percent of the women in the control group. The failure of the intervention to cause smoking cessation makes this trial essentially uninformative concerning the benefit, or lack of benefit, of smoking cessation during pregnancy. In the intervention group, 28 percent of the women reduced the number of cigarettes smoked per day, compared with 19 percent of the women in the control group. The greater reduction in cigarette consumption in the intervention group, in the absence of a difference in mean birthweight between the intervention and control groups, suggests that reducing smoking does not entirely prevent the adverse effects of smoking on birthweight.

The third randomized trial (Sexton and Hebel 1984) recruited women in a large metropolitan area from various sources. Smokers of at least 10 cigarettes per day at the beginning of pregnancy, who had not passed the 18th week of gestation, were randomly assigned to a control group that received routine advice or to a treatment group that received intensive, ongoing advice throughout pregnancy from specially trained professional staff. There were 472 women in the control group and 463 women in the treatment group. The mean birthweight of infants born to women in the control group was 3,186 g compared with 3,278 g for infants of women in the treatment group. The percentage of low birthweight infants was 8.9 in the control group and 6.8 in the treatment group. There were 11 stillbirths in the control group and 9 in the treatment group. The difference in mean birthweight was statistically significant ($p<0.05$, two-tailed test); the differences in the percentages of low birthweight and in fetal mortality were not statistically significant.

In this trial, 43 percent of the women in the treatment group had ceased smoking entirely by the eighth month of pregnancy, compared with 20 percent of the women in the control group. The intervention was, therefore, highly successful in causing substantial changes in smoking that exceeded changes in the comparison group. The investigators ruled out concomitant changes in consumption of alcohol and coffee as explanations for the increase in birthweight. Weight gain was 1.0 kg greater among the treatment group than the control group, but at least part of the difference in weight gain was a result of the higher birthweight of the infant (Sexton and Hebel 1984).

Review of these three randomized trials leads to two conclusions. First, to prevent entirely the adverse consequences of smoking on birthweight, it is necessary for women to cease smoking completely. Second, intensive interventions spanning the entire period of gestation may be necessary to effect large changes among the percentage of women who abstain from smoking entirely.

Prevalence of Smoking and Smoking Cessation During Pregnancy and Time Trends in Prevalence and Cessation

Introduction

Ideally, conclusions about the prevalence of smoking during pregnancy and trends in prevalence would be based on representative samples of pregnant women performed at regular intervals using the same methodology. Assessment of smoking cessation during pregnancy and time trends in smoking cessation should be based on representative samples of women who start pregnancy as smokers and who are monitored for smoking behavior throughout gestation. Available data fall short of these ideals.

Furthermore, available information on smoking and smoking cessation in pregnancy is based almost exclusively on self-reported behavior. Few data on the quality of self-reported smoking specifically in relation to pregnancy have been collected, and it is possible that the societal pressures against smoking during pregnancy would make underreporting more problematic than for other populations (Chapter 2). Similarly, pregnant smokers who admit to smoking might underreport their daily cigarette consumption, perhaps to a greater extent than nonpregnant smokers. The effect of underreporting of smoking and overreporting of cessation would make the data from former smokers more similar to that of continuing smokers with respect to their reproductive health outcomes. Also, smokers who reduce the amount of nicotine in their cigarettes by changing brands or those who reduce the number of cigarettes they smoke per day without quitting may compensate to maintain the same nicotine dose (US DHHS 1988).

Prevalence of Smoking and Smoking Cessation

Pertinent data on smoking during pregnancy from the 1985 National Health Interview Survey (NHIS) (NCHS 1988) are presented in Table 10. The 1985 survey focused on health promotion and disease prevention. The survey involved nearly 35,000 households and more than 90,000 persons, and the response rate was 95.7 percent. Information concerning smoking during pregnancy was obtained from all female household members aged 18 to 44 years who had had a live birth in the 5 years prior to the survey. The proportion of women who had smoked at any time during the year preceding pregnancy was 32 percent overall. Of women with less than 12 years of education, 46 percent smoked in the year preceding pregnancy, compared with 13 percent of women with 16 or more years of education. Thirty percent of married women had smoked, compared with 40 percent of formerly married women.

Patterns of smoking cessation or reduction were reported in detail for some demographic subgroups. Overall, 21 percent of women who smoked prior to pregnancy quit upon learning of their pregnancy, and an additional 36 percent reduced the number of cigarettes they smoked. Cessation (but not reduction) was strongly related to education and family income. Among women with less than 12 years of education, 12 years of education, and more than 12 years of education, 15, 20, and 32 percent quit,

TABLE 10.—Smoking and smoking cessation during pregnancy, summary of results of two surveys of national probability samples

Study (yr)	Percentage of pregnant women					
			Quit upon learning of pregnancy			
	Smoked before pregnancy	Reduced amount smoked		Educational attainment (yr)		
			All	<12	12	≥13
National Health Interview Survey[a] (1980–1985)	32	36	21	15	20	32
National Natality Survey[b] (1980)	31	27	18	10	15	22

[a]NCHS (1988).

[b]Prager et al. (1984).

respectively. The proportions for reduction in smoking were 34, 38, and 36 percent, respectively. Younger mothers were slightly more likely to quit than older mothers, and white mothers quit slightly more often than black mothers (21 vs. 18 percent). More married mothers (23 percent) than never married (19 percent) or formerly married (14 percent) mothers quit, although the proportions reducing their smoking levels were similar (36, 37, and 35 percent, respectively).

Fingerhut, Kleinman, and Kendrick (1990) also reported data on smoking in whites before and during pregnancy based on the Linked Telephone Survey, which reinterviewed 1,550 women aged 20 to 44 years who were respondents to the 1985 NHIS. This analysis confirmed the previous findings that smoking prior to pregnancy and quitting during pregnancy were strongly related to age and educational attainment. Information on amount smoked prior to pregnancy was obtained in this survey. Fifty-nine percent of women who smoked less than 1 pack per day prior to pregnancy quit smoking, compared with 25 percent of those who smoked 1 pack or more per day. Of the white women who smoked prior to pregnancy, 39 percent quit during pregnancy (27 percent when they found out they were pregnant and 12 percent later in pregnancy). This estimate of quitting during pregnancy is higher than the previous estimate of quitting from whites in this survey because it includes as quitters both women who quit upon learning that they were pregnant and those who quit later in pregnancy.

Smoking during pregnancy was also assessed in the 1980 NNS (Prager et al. 1984) (Table 10). Questionnaires were distributed to a national probability sample of married women who had had live births in 1980; the response rate was 56 percent. The restriction to married women severely compromises the generalizability of results, especially for subgroups such as blacks and youth because smoking during pregnancy

is consistently more common among unmarried mothers (Schramm 1980; Rush and Cassano 1983) and nearly one-half of black infants are born to unmarried mothers (NCHS 1982). The low response rate might have also affected the validity of the study.

Prager and associates (1984) asked women how many cigarettes they smoked per day before and after they found out they were pregnant. Among all married respondents, 31 percent smoked before pregnancy. Whites were more likely to smoke than blacks (32 vs. 25 percent). These investigators reported a strong association of smoking with age, with younger mothers more likely to smoke than older mothers. There were even more pronounced gradients with education. Among women with less than a high school education, 50 percent smoked before pregnancy, and this percentage diminished monotonically to 15 percent among women with 16 or more years of education.

Among the women in the study (Prager et al. 1984) who smoked prior to pregnancy, 18 percent quit after realizing they were pregnant. White women were somewhat more likely to quit than black women (18 vs. 13 percent). Mothers older than 35 years of age were markedly less likely to quit; only 7 percent did. Again, education had a strong association with quitting: 10 percent of mothers with less than 12 years of education quit, and the percentage increased monotonically to 24 percent among mothers with 16 or more years of education. The patterns of cessation by amount of smoking are also of interest. Women who were smoking 1 to 10 cigarettes per day at the time of pregnancy recognition were far more likely to quit than women smoking 11 or more cigarettes per day (31 vs. 12 percent). Among the heavier smokers, 27 percent reduced their consumption to 10 or fewer cigarettes per day even though they did not quit.

Williamson and associates (1989) used data from the Behavioral Risk Factor Surveillance System in 1985 and 1986 to compare smoking patterns among pregnant and nonpregnant women. Data were collected through 19,124 telephone interviews of a population-based sample of women in 26 States, with ascertainment of current pregnancy status, smoking history, and current smoking practices. Women pregnant at the time of interview were less likely to be current smokers than nonpregnant women (21 vs. 30 percent), but had a similar likelihood of ever having smoked (43 vs. 45 percent). The proportion of former smokers was thus greater among pregnant women (22 vs. 15 percent), largely accounting for the difference in current smoking patterns. This study (Williamson et al. 1989) suggests that if 30 percent of women pregnant at the time of the survey smoked prior to pregnancy, then 30 percent of smokers would have had to quit after becoming pregnant to account for the reported smoking rate of 21 percent. Among pregnant women who smoked, the mean number of cigarettes consumed per day was 12, compared with 20 cigarettes per day among nonpregnant women who smoked. These data suggest that smokers who do not quit upon becoming pregnant tend to reduce their cigarette consumption (Williamson et al. 1989).

Patterns of smoking were generally similar across demographic subgroups, with one important exception. Among unmarried women, smoking was slightly more common in pregnant than nonpregnant women (36 vs. 34 percent), implying no change in smoking among unmarried pregnant women. The absence of pregnancy-related reduction in smoking for unmarried women was due exclusively to a markedly higher smoking prevalence for white unmarried pregnant women. The results suggest that data on married mothers cannot be generalized to unmarried mothers.

A number of investigators reported smoking patterns in selected populations, such as women delivering in a particular hospital or geographic region or those receiving prenatal care at a specific clinic. Table 11 summarizes several of these studies. Although none are true probability samples, these studies provide an indication of the diversity of smoking and smoking cessation among different populations. The proportion quitting during pregnancy ranges from 6 to 49 percent.

Time Trends in Smoking and Smoking Cessation

Kleinman and Kopstein (1987) compared the pattern of smoking cessation during pregnancy from the similarly designed 1967 and 1980 NNS. Although there were some changes in the proportion of mothers who were married at the time of each of the two surveys and the characteristics of nonrespondents might have varied, the surveys provide a unique opportunity to assess temporal trends in smoking and smoking cessation during pregnancy. The percentage of mothers who smoked prior to pregnancy decreased markedly during that period, from 45 to 30 percent for white mothers and 40 to 25 percent for black mothers. The percentage of white mothers who quit after pregnancy rose from 11 to 17 percent between the two surveys, whereas the percentage of black mothers who quit decreased from 17 to 11 percent over that interval. During the interval between the surveys, the diminution of smoking during pregnancy was more pronounced for highly educated women, increasing the differential exposure to tobacco by educational status (Kleinman and Kopstein 1987).

Estimates of Attributable Risk Percent

Although several measures of attributable risk are commonly used to describe the burden of disease associated with an exposure, the most recent report of the Surgeon General (US DHHS 1989) has focused on attributable risk percent, frequently termed etiologic fraction, as the most relevant measure of the likely public health impact of smoking cessation. Calculation of the attributable risk percent uses the formula as follows:

$$ARpercent = \frac{(RR-1)p}{[(RR-1)p]+1}$$

where p is the proportion of persons with the exposure and RR is an estimate of the relative risk of the outcome in those who are exposed compared with those unexposed.

At least three different studies (Meyer, Jonas, Tonascia 1976; McIntosh 1984; Kramer 1987) estimated the relative risk of several pregnancy outcomes after reviewing the research literature. Table 12 summarizes these studies and provides estimates of attributable risk for prevalences of smoking of 20, 30, 40, and 50 percent based on the relative risk estimates from the three studies. As noted earlier, demographic subgroups of women differ markedly in smoking prevalence. Of those women with less than a high school education, 50 percent smoked during pregnancy; of those women with some college education , 20 percent smoked during pregnancy (NCHS 1988). Approximately 30 percent of married women and 40 percent of unmarried women smoked prior to

TABLE 11.—Patterns of smoking cessation during pregnancy among selected populations

Reference	Location	Source	Years	% Smoking initially	% Smokers quitting[a]	% Smokers reducing[a]
Lowe (1959)	Birmingham, UK	Maternity hospitals	1958	43	20	NR
Schwartz et al. (1972)	Paris	Hospitals	1963–69	17	31	10
Butler, Goldstein, Ross (1972)	United Kingdom	National survey	1958	38	18	NR
Hook (1976)	New York State	Not stated	NR	50	NR	24
Papoz et al. (1982)	Paris	Maternity hospital	1976–79	37	49	NR
Ershoff et al. (1983)	Southern California	HMO	1980	22	38	NR
Pulkkinen (1985)	Finland	Prenatal care clinic	1980	NR	28	NR
Windsor et al. (1985)	Birmingham, AL	Maternity hospital	1981–82	29	22	NR
MacArthur, Newton, Knox (1987)	West Midlands, UK	Maternity hospital	1981–82	29	6	19
MacArthur and Knox (1988)	West Midlands, UK	Maternity hospital	NR	32	17	NR

NOTE: NR=not reported; HMO=health maintenance organization.

[a]Quitting or reducing by the end of the fourth month (16 wk).

TABLE 12.—Summary of studies that estimated relative risk of various pregnancy outcomes for smoking based on a "synthesis" of the literature, and attributable risk percent based on several estimates of the prevalence of smoking during pregnancy

Reference	p[a]	Perinatal mortality		Low birthweight		Preterm delivery	
		RR	AR%	RR	AR%	RR	AR%
Meyer, Jonas,	0.20	1.21[b]	4	1.99[b]	17	1.32[b]	6
Tonascia	0.30		6		23		9
(1976)	0.40		8		28		11
	0.50		10		33		14
McIntosh	0.20	1.25	5	1.81	14	1.45	8
(1984)	0.30		7		19		12
	0.40		9		24		15
	0.50		11		29		18
Kramer	0.20	NR	—	2.42	22	1.41	8
(1987)	0.30		—		30		11
	0.40		—		36		14
	0.50		—		42		17

NOTE: RR=relative risk; AR=attributable risk; NR=not reported.

[a]Prevalence of smoking.

[b]Averaging across studies.

pregnancy (NCHS 1988). The most recent estimates suggest that about 25 percent of U.S. women smoke throughout pregnancy (NCHS 1988).

The relative risk estimates for perinatal mortality and preterm delivery are remarkably consistent, especially considering that these authors conducted independent syntheses of the literature. Estimates of the relative risk of low birthweight ranged from 1.81 (McIntosh 1984) to 2.42 (Kramer 1987), probably because of differences in the number of studies used to derive the estimate. For this reason, attributable risk percent for a given prevalence of smoking is more variable for low birthweight than for perinatal mortality and preterm delivery.

Based on data that indicate that about 25 percent of U.S. women smoke throughout pregnancy, it can be estimated that 5 to 6 percent of perinatal deaths, 17 to 26 percent of low birthweight births, and 7 to 10 percent of preterm deliveries could be prevented by elimination of smoking during pregnancy. In groups with a 50-percent prevalence of smoking, such as women with less than a high school education, approximately 10 to 11 percent of perinatal deaths, 29 to 42 percent of low birthweight births, and 14 to 18 percent of preterm deliveries might be prevented by elimination of smoking during pregnancy. These contributions to adverse pregnancy outcome are sizable, and smoking is probably the most important modifiable cause of poor pregnancy outcome among women in the United States (Kramer 1987).

Introduction

The significance of menopause extends beyond marking the end of female reproductive potential. The age at which menopause occurs also may have implications for the risks of osteoporotic fractures, ischemic heart disease, and cancers of the reproductive system. Thus, the effect of smoking on the age of menopause could have potentially broad health implications.

In fact, an early natural menopause has been observed consistently among women who smoke cigarettes. As summarized in Table 13, the major studies addressing this topic have indicated that currently smoking women cease menstruating from 1 to 2 years earlier than otherwise similar nonsmokers. Expressed as relative risk, women aged 44 to 54 years who smoke become menopausal at about twice the rate of never smokers (Willett et al. 1983; Bailey, Robinson, Vessey 1977; Hartz et al. 1987; Andersen, Transbol, Christiansen 1982; Baron 1990).

Several features of the data suggest that this is a causal relationship. By using both cohort and cross-sectional methodology with a variety of subject populations, the results have been replicated repeatedly in studies in several areas of the United States and Europe. Dose–response effects have generally been found, with heavy smokers experiencing an even earlier menopause on average than light smokers. However, these trends have not always been assessed with formal tests of statistical significance in the reports describing the data. Several studies demonstrating this association have controlled for potential covariates. That premenopausal smokers may be more likely than nonsmokers to have a hysterectomy does not appear to explain the relationship (Krailo and Pike 1983).

Pathophysiologic Framework

There are at least three ways in which cigarette smoking could lead to an early natural menopause. Experiments with laboratory rodents indicate that the polycyclic aromatic hydrocarbons found in cigarette smoke may be directly toxic to ovarian follicles (Mattison 1980). Mattison and colleagues found that intraperitoneal injection of benzo(a)pyrene, 3-methylcholanthrene, or 7,12-dimethylbenz(a)anthtracene led to ovarian follicular atresia (Mattison and Thorgeirsson 1978, 1979; Gulyas and Mattison 1979). Earlier uncontrolled studies of prolonged exposure of mice to cigarette smoke led to similar findings (Essenberg, Fagan, Malerstein 1951), which were also seen in a later controlled study of rats (Subbarao 1988). However, other investigators failed to find ovarian atrophy in rodents chronically exposed to cigarette smoke (Haag, Larson, Weatherby 1960; Dontenwill et al. 1973a), and in most studies, parenteral nicotine or tobacco extract has had minimal effect on the ovaries of experimental animals (Essenberg, Fagan, Malerstein 1951; Thienes 1960; Larson, Haag, Silvette 1961; Larson and Silvette 1968).

The other two postulated mechanisms for premature menopause do not involve direct ovarian toxicity. Cigarette smoking may interfere with luteinizing hormone release at

TABLE 13.—Summary of studies reporting relationship of cigarette smoking and age at natural menopause

Reference	Source and number of subjects	Covariates considered	Difference in median menopausal ages[a] (yr)
Jick, Porter, Morrison (1977)	2,143 hospital patients in Boston area	Parity, marital status, coffee/tea/alcohol, hospital service, diagnosis	1.7
	1,391 hospital patients in 7 countries	Same as above	1.3[b]
Daniell (1978)	500 patients	Weight	2.0[c]
Bailey, Robinson, Vessey (1977)	733 health screenees	None	1.3[b]
McNamara et al. (1978)	1,553 general population subjects	None	0.8[c]
Lindquist and Bengtsson (1979)	873 general population subjects	Weight	1.2[b]
Kaufman et al. (1980)	656 hospital patients	Parity, ponderal index, age first smoked, geographic region	1.7[c]
Adena and Gallagher (1982)	10,995 health screenees	Weight, alcohol intake, drug taking	1.0
Willett et al. (1983)	66,663 nurses	Height, weight, diabetes, hypertension, age of menarche, nulliparity	1.4
McKinlay, Bifano, McKinlay (1985)	5,350 general population subjects	None	1.7
Everson et al. (1986)	261 population subjects	Passive smoking	1.1
Hiatt and Fireman (1986)	5,346 HMO health screenees	None	0.95[c]
Stanford et al. (1987)	3,545 breast cancer screenees	None	0.3
Brambilla and McKinlay (1989)	2,565	Education, income	1.5

NOTE: HMO=health maintenance organization.

[a]Median menopausal age among nonsmokers minus median menopausal age among smokers.

[b]Computed by Adena and Gallagher (1982).

[c]Difference in mean menopausal ages.

least in rodents exposed to parenteral nicotine or cigarette smoke (Andersson et al. 1980; Andersson et al. 1984; Andersson et al. 1988; Eneroth et al. 1977a,b; Kanematsu and Sawyer 1973; Blake, Norman, Sawyer 1974; Blake 1974; Blake et al. 1972a,b; McLean, Rubel, Nikitovitch-Winer 1977). This effect appears to be due to a nicotinic effect on neurotransmitter release. A return to a more normal function after the end of exposure to smoke or nicotine has not been documented, but it seems likely that such a nicotinic effect on the brain would not be permanent. Therefore, it is possible that in humans, smoking could cause a reversible interference in the pituitary-ovarian axis, which could lead to a cessation of menses. Several investigators found that smoking has been associated with menstrual irregularity earlier in reproductive life (Wood 1978; Pettersson, Fries, Nillius 1973; Brown, Vessey, Stratton 1988; Hammond 1961).

Smoking has also been associated with disturbances of estradiol metabolism. Michnovicz and colleagues (1986) found that premenopausal smokers tend to metabolize estradiol through pathways producing more catechol-estrogen metabolites than nonsmokers. This change would be expected to result in a relative antiestrogenic influence because of the lack of estrogenic potency of the catechol-estrogens compared with the estrogenic metabolites, such as estriol, which are produced in larger amounts in nonsmokers. There is also evidence that nicotine may inhibit aromatase, an enzyme important in the synthesis of estrogens (Barbieri, McShane, Ryan 1986; Barbieri, Gochberg, Ryan 1986). Again, the recovery of normal enzymatic function after cessation of smoking has not been studied. However, it is postulated that these or similar disturbances could result in enough antagonism of estrogen effect to cause an early cessation of menstrual cycling in women already in the perimenopausal years (Baron, LaVecchia, Levi 1990)

Studies of Former Smokers

Former smokers experience menopause only slightly earlier than never smokers (Table 14). In a study of hospitalized women, Jick, Porter, and Morrison (1977) found that former smokers had a median age at menopause between that of never smokers and that of women currently smoking half a pack of cigarettes per day. Kaufman and coworkers (1980) reported on hospitalized women aged 60 to 69 years. Data from 10 women who stopped smoking before age 35 indicated that the mean age at menopause was 0.2 years earlier than in never smokers, after adjustment for parity and body habitus (Kaufman et al. 1980). In a cross-sectional study of women attending a screening clinic, Adena and Gallagher (1982) found ex-smokers to have a median age of natural menopause 0.3 years earlier than never smokers. Finally, Hiatt and Fireman (1986) found among a group of enrollees in a prepaid health plan attending a screening clinic that ex-smokers reached menopause about 0.5 years earlier than never smokers. Thus, natural menopause appears to occur, at most, 6 months earlier in ex-smokers than in never smokers.

Limited findings on relative risk of early menopause in former smokers are available (Willett et al. 1983; Baron, LaVecchia, Levi 1990). From data presented by Lindquist and Bengtsson (1979) regarding 50-year-old women, it can be calculated that compared with never smokers, former smokers had a relative risk of early menopause of 1.8

TABLE 14.—Summary of studies of age at natural menopause among former smokers

Reference	Number of ex-smokers	Covariates considered	Findings
Jick, Porter, Morrison (1977)	439	None	Ex-smokers had menopause between those of current light smokers and never smokers
Lindquist and Bengtsson (1979)	30	None	Odds ratio of being menopausal for ex-smokers vs. never smokers was 1.8
Kaufman et al. (1980)	10	Parity, region, Quetelet's Index	Mean age at menopause was 0.2 yr earlier among ex-smokers than among never smokers
Adena and Gallagher (1982)	NR	None	Median age of menopause was 0.3 yr earlier among ex-smokers than among never smokers
Willett et al. (1983)	16,034	Age, weight, nulliparity	Odds ratio of being menopausal for current smokers vs. never smokers was 1.10
Hiatt and Fireman (1986)	576	None	Mean age at menopause was 0.5 yr earlier among ex-smokers than among never smokers

NOTE: NR=not reported.

(95-percent confidence interval, (CI), 1.1–4.7). In a prospective study of American nurses, Willett and coworkers (1983) found ex-smokers to have a relative risk of early menopause of 1.1 (95-percent CI, 0.98–1.23) compared with never smokers after adjustment for age, weight, and nulliparity. In this study, those who stopped smoking in the 2 years previously retained a modest increase in risk of early menopause (RR=1.4); after a longer period of abstinence, there was no effect associated with previous smoking (Willett et al. 1983).

All the investigations of smoking and menopause have relied on self-report of menstrual status and smoking history. It is unlikely that misclassification with regard to these features would seriously distort the findings regarding current smoking, but the results for former smoking may be more susceptible to artifact. In particular, some of the study participants who claimed to be former smokers might actually have continued to smoke, or they might have quit for health reasons related to an early natural

menopause. Like current smokers, former smokers may be more likely to be passively exposed to passive smoking than never smokers, thus possibly affecting menopausal age. These factors would tend to lead to an exaggeration of the apparent impact of former smoking on menopausal age (Chapter 2). Therefore, the results summarized above may overstate the degree to which former smoking is associated with any disturbance in menopausal age.

It appears that age at menopause in former smokers is closer to that of never smokers than to current smokers, and the data are consistent with a decline in the risk of early menopause with the cessation of smoking. The effect of smoking on menopausal age may be partly or wholly reversible with cessation of smoking during the premenopausal years. However, some pertinent data are lacking. Most of the studies did not consider how long it takes after cessation of smoking for the risk of early natural menopause to decrease. No studies have verified that the women who stopped smoking had a lifetime smoking exposure similar to that of women who continued smoking.

PART II. MALE

Introduction

Cigarette smoking has been considered to be associated with impairment of male sexual functioning, and tobacco abstinence has been recommended for men attempting to maximize sexual performance (Larson, Haag, Silvette 1961; Sterling and Kobayashi 1975; Ochsner 1971a,b). An association between smoking and impaired sexual performance among men has been publicized in the lay press (Reuben 1988). Although some data provide evidence for this association, they are inconclusive.

Pathophysiologic Framework

Three general types of mechanisms have been proposed to explain the harmful effect of cigarette smoking on sexual performance, impotence, and sperm quality. First, smoking may expose the testes to compounds that are directly toxic to the sperm-producing germinal epithelium, to early sperm forms, or to the hormone-producing Leydig cells. The effects on sperm may be a manifestation of a genotoxic effect of cigarette smoke constituents (Obe and Herha 1978; DeMarini 1983).

Second, smoking causes atherosclerotic peripheral vascular disease (Chapter 6); this may translate into a diminished vascular supply to the genitals, as reflected by the penile brachial index (PBI) and other vascular measurements. A diminished vascular supply to the genitals would compromise sexual performance and spermatogenesis and hormone production. Although atherosclerosis is often considered a fixed lesion, several studies have suggested that atherosclerotic plaques may regress with appropriate lifestyle changes (Barndt et al. 1977; Nikkilä 1980; Kramsch et al. 1981; Chapter 6). However, no studies have been conducted on the effect of smoking cessation on regression of atherosclerotic lesions.