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**CHAPTER 5**

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**Pregnancy**

## Contents

	<i>Page</i>
Introduction .....	83
Effect on Birth Weight .....	83
Effect on the Outcome of Pregnancy .....	83
Congenital Malformations .....	87
Cancer in Children Born to Smoking Mothers .....	87
Long-Term Effects on Children Born to Smoking Mothers ..	88
Experimental Studies .....	88
Summary .....	89
References .....	89

## LIST OF TABLES

Table 1.—Frequency of abortion and cigarette consumption	85
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## INTRODUCTION

The 1971 report, "The Health Consequences of Smoking" (23), summarized the relationship between smoking and pregnancy as follows:

Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birth weight and an increased incidence of prematurity, defined by weight alone. There is strong evidence to support the view that smoking mothers have a significantly greater number of unsuccessful pregnancies due to stillbirth and neonatal death as compared to nonsmoking mothers. There is insufficient evidence to support a comparable statement for abortions. The recently published Second Report of the 1958 British Perinatal Mortality Survey, a carefully designed and controlled prospective study involving large numbers of patients, adds further support to these conclusions.

New epidemiological, experimental, and pathologic studies lend support to the foregoing statements.

## EFFECT ON BIRTH WEIGHT

Analysis of data from more than 100,000 births has shown that infants of mothers who smoke during pregnancy have a mean birth weight of 6.1 ounces (173 grams) less than infants born to nonsmoking mothers (23). Several recent studies confirm this relationship (1, 2, 6, 7, 10, 13, 15, 18, 25).

## EFFECT ON THE OUTCOME OF PREGNANCY

New studies have been published concerning the effect of maternal smoking on the outcome of pregnancy.

Kullander and Källén (13) performed a prospective study in Sweden involving 6,363 pregnant women. These women completed several questionnaires during the course of their pregnancy, and in this manner specific information was obtained on smoking habits for the entire pregnancy. Forty-four percent of the women smoked cigarettes during pregnancy and 97 percent of these smoked during the whole pregnancy.

Stillbirths, neonatal deaths, and deaths occurring before one year of age were recorded to determine a "total death risk." This risk was approximately 60 percent higher for children born to smoking mothers as compared to those born to nonsmoking mothers.

Deaths occurring before one week of age and also deaths taking place between the age of one week and one year were significantly more frequent in children born to smoking mothers. Among children dying before one week of age, significantly more cases of abruptio placentae were found in smoking mothers than in nonsmoking mothers. The higher level of neonatal mortality in children born to smoking mothers was confined to those weighing more than 2,500 grams. Live-born infants weighing less than 2,500 grams had equally high neonatal mortality rates whether they were born to smoking or nonsmoking mothers. The stillbirth rate was greater in smoking mothers than in nonsmoking mothers, but the difference was not statistically significant.

An overall increased risk of spontaneous abortion among smoking women was found, but this was primarily due to an association between unwanted pregnancy and smoking. The authors found that significantly ( $P < .001$ ) more women with unwanted pregnancies were smokers than women with wanted pregnancies; in addition, spontaneous abortions were significantly ( $P < .001$ ) more frequent among women with unwanted pregnancies than among women with wanted pregnancies. When correction was made for the mothers' acceptance of pregnancy, the contribution of maternal smoking to spontaneous abortion was of only borderline significance.

Also in the Kullander and Källen study (13), a decreased frequency of preeclampsia among smoking mothers was noted. Maternal smoking had no effect on the mean Apgar score of surviving, non-malformed children.

A prospective study from Sweden of abortions in 4,312 pregnancies was reported by Palmgren and Wallander (17). Only those women who smoked throughout pregnancy were considered smokers. The lowest abortion rate was found among nonsmokers, 7.8 percent, while the highest rate was found among heavy smokers, 14.5 percent (table 1). The difference is statistically significant ( $P < .001$ ). Heavier smokers appeared to abort earlier in pregnancy. A history of previous abortion was obtained twice as often in heavy smokers as in nonsmokers.

Yerushalmy reported in 1964 on pregnancies occurring in women participating in the Kaiser Health Plan of the San Francisco-Oakland area (24). The 1971 report, "The Health Consequences of Smoking" (23), commented in detail on that report. Recently, Yerushalmy published data on 13,083 pregnancies occurring in this plan between 1960 and 1967, which included the 6,800 cases previously reported (24, 25).

TABLE 1.—*Frequency of abortion and cigarette consumption.*

Result of the pregnancy	Nonsmokers	≤10 cigarettes	>10 cigarettes	Total
Abortion	177 7.8%	148 9.1%	60 14.5%	385 8.9%
Delivery	2,087 92.2%	1,486 90.9%	354 85.5%	3,927 91.1%
Total	2,264	1,634	414	4,312

SOURCE: Palmgren, B., Wallander, B. (17).

As in the 1964 study, he again found an increase in the incidence of low birth weight infants (less than 2,500 grams) among smoking mothers. These small infants had a significantly lower neonatal mortality rate and fewer congenital anomalies than the small infants born to nonsmoking mothers. The neonatal mortality rate for single, live-born infants born to white, smoking mothers was 11.3/1000, while that for single, live-born infants born to white, nonsmoking mothers was 11.0/1000; the difference is not significant.

Taylor analyzed Yerushalmy's data for the probability of fetal death and found no difference between smoking and nonsmoking mothers (22).

Some of these findings are different from those reported in the other recent, large-scale prospective studies (5, 13, 17, 19), and some of the differences may be a consequence of the definition of "smoker" used. In the study of Kullander and Källen (13), multiple interviews were performed during pregnancy which allowed more precise separation of the pregnant women into smokers and nonsmokers. In the study reported by Palmgren and Wallander (17), only those women who smoked throughout pregnancy were considered smokers. The British Perinatal Mortality Study (5), which was discussed in the 1971 report, "The Health Consequences of Smoking" (23), defined "smokers" as those women who smoked regularly after the fourth month of pregnancy. The smoking history was obtained shortly after delivery of the infant.

In contrast, Yerushalmy (25) defined "smokers" as women who were smoking one or more cigarettes a day during the pregnancy, and "nonsmokers" as women who never smoked and those who stopped smoking either before or during the pregnancy. Because the smoking history was obtained only once, usually early in pregnancy, some of the women who were classified as smokers could have gone through a significant portion of their pregnancy as nonsmokers, and similarly some of the women who were classified as

nonsmokers could have gone through a significant portion of their pregnancy as smokers. If smoking by pregnant women increases the risk of an unsuccessful pregnancy, an imprecise separation of pregnant women into smokers and nonsmokers would tend to diminish the magnitude of any differences found. One Swedish study (13) and the British Perinatal Mortality Study (5) seemed to be at variance in statements about the frequency with which smoking habits vary from one portion of the pregnancy to another. If this is a culturally determined phenomenon, there is no way of estimating the extent to which it applies to the patients participating in the Kaiser Health Plan described by Yerushalmy.

MacMahon, et al. (14) commented on Yerushalmy's analysis of mortality rates in low birth weight infants. They observed that there are "... factors that affect birth weight without influencing mortality; for example, females have lower birth weights than males but not the higher mortalities that might be predicted for them on that account. If cigarette smoking is another such factor, the explanation of the higher weight-specific mortalities for nonsmokers becomes immediately clear: it is an artifact of the analysis. It is meaningful to compare category-specific rates only when the specification of the category has the same implication for each of the populations compared."

Perinatal mortality rates were similar in infants born to smoking and nonsmoking mothers in a recent prospective investigation of 1,300 pregnancies from New Zealand (1). Women were classified as smokers or nonsmokers during their first "booking" at an antenatal clinic, and this was not later amended. This method of classification is similar to that used in the Yerushalmy study.

Comstock, et al. (6, 7) have reported in 1967 and 1971 on the relationship of maternal smoking to the outcome of pregnancy. In their studies, all perinatal deaths and samples of live births occurring during a 10-year period among children whose mothers were residents of Washington County, Maryland, were matched against the records of a special census based on a household interview taken in 1963. Maternal smokers were defined as women who were smoking in 1963 and who had started to smoke prior to the pregnancy in question; maternal nonsmokers were women who denied ever having smoked. When this study is compared to previously cited studies (5, 13, 17), the data on the smoking status of the mothers during pregnancy are imprecise, which limits their value.

In the 1967 study (6), maternal smoking was associated with an increased risk of mortality for the child, both in the neonatal period and for several years thereafter; however, this effect was thought to be related to factors such as adequacy of prenatal or postnatal environment and care, rather than a direct effect of maternal smoking. Stillbirth rates were similar for smokers and nonsmokers.

The more recently published study (7) includes a 32 percent sample of live-born, low birth weight infants and a 3 percent sample of live-born, larger infants born during the 10-year period preceding the census. The total births represented by these samples were 4,641 to smokers and 7,646 to nonsmokers. The neonatal mortality rate, when adjusted for environmental and socioeconomic factors, was approximately one-third higher among infants born to smoking mothers than among those born to nonsmoking mothers (7). The categories of asphyxia, atelectasis, and immaturity accounted for the greater neonatal mortality among infants born to smoking mothers as compared to those born to nonsmoking mothers (7).

#### CONGENITAL MALFORMATIONS

As noted in the 1971 report, "The Health Consequences of Smoking" (23), the possible teratogenic effect of maternal smoking has not been adequately evaluated. Additional studies have been published in the interim, but rather than investigating congenital malformations in both stillborn and live-born infants, most of the recent studies have dealt only with live-born infants.

Fedrick, et al. (8) analyzed data from the large British Perinatal Mortality Study for the incidence of congenital heart disease in stillborn and live-born infants of smoking and nonsmoking mothers. An incidence of 7.3/1000 births was found in infants born to smoking mothers as compared to 4.7/1000 births for infants born to nonsmoking mothers, a statistically significant difference ( $P < .001$ ).

Kullander and Källén (13) noted no teratogenic effect of maternal smoking in children dying before one year of age or in children surviving one year of age. However, they observed that published studies have been too small to exclude this possibility.

In a study of perinatal death occurring in infants weighing more than 1,000 grams, Bailey (1) found that maternal smoking did not lead to an increased incidence of congenital anomalies.

Yerushalmy (25) reported only on live-born infants weighing less than 2,500 grams and found significantly fewer ( $P < .02$ ) anomalies among infants born to smoking mothers.

Comstock, et al. (7) found fewer than the expected number of congenital anomalies among live-born infants of smoking mothers.

#### CANCER IN CHILDREN BORN TO SMOKING MOTHERS

Neutel and Buck (16) studied the relationship between maternal smoking during pregnancy and the development of cancer in the offspring. The base population was obtained from the British and Ontario Perinatal Studies and consisted of 89,302 babies who sur-

vived at least seven days. There were 65 cancer deaths and 32 cancer survivors in the period from birth to a minimum of 7 and a maximum of 10 years of age. For cancer of all sites, the children of smokers had a relative risk of 1.3. The authors concluded: "Although these results make it most unlikely that *in utero* exposure to tobacco smoke has a broadly carcinogenic effect on the fetus, a response confined to one tissue or expressed over a narrow age range cannot be ruled out."

#### LONG-TERM EFFECTS ON CHILDREN BORN TO SMOKING MOTHERS

Goldstein (9) analyzed data from the British Perinatal Mortality Study to determine factors influencing the height of 7-year-old children. In the 1958 study, information was collected on 16,994 singleton births. In 1965, heights were measured "to the nearest inch" on 13,127 of these children who could be followed up. The data were analyzed for the influence of parity, birth weight, length of gestation, maternal age, maternal height, social class, number of younger siblings, and maternal smoking habits during pregnancy. Allowance was made for the sex and age of the child at the time of measurement. The author's conclusions included the following: "After allowing for the other variables, the children of mothers who smoked 10 or more cigarettes a day after the 4th month of pregnancy, are on average about 1.0 cm shorter at age seven than the children of mothers who did not smoke."

#### EXPERIMENTAL STUDIES

Becker and Martin (3) continued their experiments concerning the effect of nicotine on pregnant rats. Offspring of rats given nicotine weighed significantly less at birth than saline-injected controls. There were fewer live births among the nicotine-injected rats.

Kelly and Roy (12), using cinephotomicrography, demonstrated that nicotine crosses the mouse placental barrier in amounts adequate to produce a measurable cardiovascular response.

Stalhandske, et al. (21) studied the *in vitro* metabolism of nicotine in livers of fetal, young, and adult mice. Cotinine was found to be the major metabolite at all ages investigated.

Using radioactive compounds, Sieber and Fabro (20) identified a variety of drugs in the preimplantation blastocyst and in uterine secretions of pregnant rabbits. In animals receiving dose levels of nicotine comparable to that encountered in man, significant amounts of radioactivity were found in the preimplantation blastocyst. A markedly higher concentration of radioactivity was observed in uterine secretion than in maternal plasma.

Juchau (11) studied the levels of benzpyrene hydroxylase in the placentas of smoking and nonsmoking women obtained both early in pregnancy and at term. This enzyme hydroxylates benzo (a) pyrene, a carcinogenic hydrocarbon found in tobacco smoke. Previous studies had shown that placentas, obtained at term from smoking women, have a greater ability to hydroxylate benzo (a) pyrene than the placentas from nonsmokers (23). Juchau corroborated this, but also found very low levels in placental tissues obtained from healthy smokers during first trimester dilatation and curettage or hysterotomy for therapeutic abortion. This lack of significant placental drug metabolizing activity during the first trimester was interpreted as a possible hazard to the fetus, particularly if the substance were active in the unmetabolized form. Enzyme levels were undetectable in placental homogenates of nonsmokers at 8 to 16 weeks gestation.

The carcinogenic effect on the newborn of rats receiving benzo (a) pyrene during the latter half of pregnancy was studied by Bulay and Wattenberg (4). An increased incidence of pulmonary adenoma and skin papilloma was observed.

#### SUMMARY

Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birth weight and an increased incidence of prematurity, defined by weight. There is increasing evidence to support the view that women who smoke during pregnancy have a significantly greater risk of an unsuccessful pregnancy than those who do not.

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## **CHAPTER 6**

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### **Gastrointestinal Disorders**

## Contents

	<i>Page</i>
Highlights of Current Gastrointestinal Information . . . . .	98
References . . . . .	98

## GASTROINTESTINAL DISORDERS

The 1971 report, "The Health Consequences of Smoking" (4), summarized the relationship between smoking and peptic ulcer as follows:

Cigarette smoking males have an increased prevalence of peptic ulcer disease and a greater peptic ulcer mortality ratio. These relationships are stronger for gastric ulcer than for duodenal ulcer. Smoking appears to reduce the effectiveness of standard peptic ulcer treatment and to slow the rate of ulcer healing.

Studies of the effect of smoking on gastric secretion in patients with peptic ulcer and normal controls have produced conflicting reports (4). Recently, Wilkinson and Johnston (5) reported a significant inhibition of pentagastrin-stimulated gastric acid secretion after cigarette smoking by normal volunteers, while Debas, et al. (1) found no significant overall change. Wilkinson and Johnston also studied patients with gastric and duodenal ulcers in whom a significant inhibition of pentagastrin-stimulated gastric secretion was observed after the patients smoked one or two cigarettes over a period of 10 to 15 minutes.

A study by Konturek, et al. (3) suggests that alterations in pancreatic and biliary secretion may be responsible for the relationship between smoking and peptic ulcer. Nicotine was infused in mongrel dogs in doses corresponding to amounts absorbed from smoking up to four cigarettes in one hour. In the pancreas, nicotine inhibited the secretin-stimulated secretion of both fluid and bicarbonate, and the degree of inhibition was dose-related. Spontaneous biliary secretion of bicarbonate was also depressed by the drug. Nicotine had no effect on gastric secretion of acid, gastric mucosal blood flow, or the mucosal barrier to hydrogen or sodium ions. This inhibition of pancreatic and hepatic bicarbonate secretion may deprive the duodenum of sufficient alkaline secretion to neutralize gastric acidity and may be one biomechanism linking cigarette smoking and peptic ulcer.

Dennish and Castell (2) noted the clinical association between cigarette smoking and heartburn. To investigate the biomechanism of this relationship, lower-esophageal sphincter pressure determinations were made before and after smoking in six normal male volunteers. All of the volunteers were cigarette smokers. In each

subject after the onset of cigarette smoking, there was a rapid decrease in lower-esophageal sphincter pressure from the basal level. This diminution in sphincter pressure persisted until smoking was stopped, at which time the pressure returned rapidly toward normal. Mean basal pressure was  $19.6 \pm 2.1$  ( $\pm 1$  S.E.) mmHg. and mean pressure during smoking was  $11.4 \pm 2.2$  mmHg. The difference between these pressures is statistically significant ( $P < .001$ ). No changes were noted when volunteers puffed on unlit cigarettes. Variable responses were noted when volunteers smoked cigars and pipes. The investigators concluded that cigarette smoking decreases the effectiveness of the lower-esophageal sphincter as a barrier against gastroesophageal reflux.

#### HIGHLIGHTS OF CURRENT GASTROINTESTINAL INFORMATION

In addition to the summary statement cited at the beginning of this section, the following observations have been made:

1. A possible link between cigarette smoking and peptic ulcer has been demonstrated in dogs in which nicotine was found to inhibit pancreatic and hepatic bicarbonate secretion. This could lead to peptic disease by depriving the duodenum of sufficient alkaline secretion to neutralize gastric acidity.
2. An investigation in human volunteers has suggested that cigarette smoking decreases the effectiveness of the lower-esophageal sphincter as a barrier against gastroesophageal reflux.

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## **CHAPTER 7**

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**Allergy**