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CHAPTER 8
SMOKING CESSATION AND REPRODUCTION

CONTENTS

PART I. FEMALE

Pregnancy and Pregnancy Outcome

Introduction

Since the late 1940s, cigarette smoking during pregnancy has been linked with poor pregnancy outcome (Bernhard 1949; Athayde 1948). Adverse effects of smoking on pregnancy began to receive considerable attention after publication of the results of a study of 7,499 pregnant women in San Bernardino County, CA, in which the rate of prematurity, defined as birthweight less than 2,500 g, was found to be about twice as high among smokers as among nonsmokers during pregnancy (Simpson 1957).

Early reports of the Surgeon General (US DHEW 1971, 1973, 1978) concluded that maternal smoking during pregnancy retards fetal growth and is a probable cause of late fetal and infant mortality (US DHEW 1973). The 1977 Report of the Surgeon General (US DHEW 1978) concluded that smoking during pregnancy has dose–response relationships with abruptio placentae, placenta previa, bleeding during pregnancy, premature and prolonged rupture of the membranes, and preterm delivery. The 1979 and 1980 Reports of the Surgeon General (US DHEW 1979; US DHHS 1980) comprehensively reviewed information on the association of maternal smoking with pregnancy outcome and further concluded that the risk of spontaneous abortion increases with the amount of smoking and that the risk of sudden infant death syndrome (SIDS) is increased by maternal smoking during pregnancy. The 1980 Report (US DHHS 1980) also indicated the possibility of a link between cigarette smoking and impaired fertility.

Two earlier reports of the Surgeon General (US DHEW 1979; US DHHS 1980) concluded that mean gestational duration is not affected by maternal smoking and that data are not sufficient to support a conclusion that maternal smoking increases, decreases, or has no association with risk of congenital malformations.

This Section reviews observational studies of smoking cessation and the following reproductive outcomes: fertility and infertility; ectopic pregnancy and spontaneous abortion; fetal, neonatal, and perinatal mortality; birthweight and gestational duration; and complications of pregnancy. Three randomized trials of smoking cessation and pregnancy outcome are described and discussed in detail. Information on the prevalence of smoking during pregnancy and time trends in prevalence is presented, along with estimates of the attributable risk of several pregnancy outcomes. SIDS and congenital malformations are not considered because of the limited information on smoking cessation.

Pathophysiologic Framework

The effects of smoking that might mediate adverse effects on the developing fetus and on fertility, fetal loss, and pregnancy complications have been reviewed in other publications (Longo 1982; Mattison 1982; US DHHS 1980). These reviews are summarized with attention to the temporal course of the relation between exposure to

cigarette smoking and pregnancy outcome as well as the distinction between reversible and irreversible effects of smoking. Reversible effects would be expected to result in similar risks for never smokers and former smokers, whereas irreversible effects would be expected to lead to different risks in both current and former smokers compared with never smokers.

Several pathways have been postulated by which tobacco smoke might adversely affect fertility (Mattison 1982) (Table 1). These include disturbance of hypothalamic–pituitary function, interference with motility in the female reproductive tract (Chow et al. 1988), and impairment of implantation, all of which are thought to be reversible consequences of exposure to absorbed chemicals in tobacco smoke (principally nicotine). It has also been suggested that smoking results in oocyte depletion through direct toxicity (Mattison 1980), which would have irreversible consequences for fertility. Chow and colleagues (1988) postulated that altered immune function (Hersey, Prendergast, Edwards 1983) may predispose smokers to pelvic inflammatory disease, which in turn can result in permanent scarring and occlusion of the fallopian tubes. Alterations in the neuroendocrine control of ovulation have been suggested to account for increased amenorrhea reported among smokers (Pettersson, Fries, Nillius 1973); this mechanism, as an effect of smoking on fertility, would be reversible.

TABLE 1.—Possible mechanisms for the effect of smoking on pregnancy and pregnancy outcome

Outcome	Possible mechanism
Reduced fertility	Hormonal effects Impaired tubal motility Impaired implantation Oocyte depletion Altered immunity leading to pelvic inflammatory disease
Spontaneous abortion	Nicotine toxicity
Reduced birthweight	Impaired weight gain Nicotine toxicity CO toxicity Increased cyanide leading to impaired vitamin B_{12} metabolism Hypoxia due to increased levels of CO or to vasoconstriction of umbilical artery

NOTE: CO=carbon monoxide.

Mechanisms for an effect of cigarette smoking on spontaneous abortion have not been clearly defined, partly because so little is known about the pathophysiologic basis for spontaneous abortion. The causes of spontaneous abortion are broadly divided into genetic and nongenetic causes (Kline 1984). Because smoking seems to have its primary impact on chromosomally normal spontaneous abortions (Kline 1984; Alberman et al. 1976), nongenetic pathways are implicated for smoking (Table 1).

Most attention has been focused on the mechanisms mediating a reduction of fetal growth among smokers (Table 1). An indirect, nutritionally based mechanism in which smokers are postulated to eat less and gain less weight during pregnancy, thus delivering smaller infants, has been prominent in discussions of fetal growth retardation in smokers (Papoz et al. 1982; Rush 1974; Meyer 1978; Davies and Abernethy 1976). This subject has been reviewed in depth in previous reports of the Surgeon General (US DHEW 1979; US DHHS 1980) and more recently by other researchers (Werler, Pober, Holmes 1985). Differences in weight gain do not entirely explain fetal growth retardation in smokers because differences in weight gain during pregnancy between smokers and nonsmokers are very small and have not been observed consistently and because a relationship between growth retardation and smoking persists after adjusting for maternal weight gain.

In this context, however, the studies of weight gain in women who quit smoking during pregnancy are of interest. Pulkkinen (1985) found that women who quit smoking during the first trimester gained more weight than nonsmokers or continuing smokers (1.0 vs. 1.3 kg average difference, respectively). Kuzma and Kissinger (1981) also found that women who quit smoking during pregnancy gained more weight compared with women who did not smoke during pregnancy (average difference of 4.7 kg) and women who smoked throughout pregnancy (average difference of 5.6 kg). Also, women who quit smoking before the onset of pregnancy were reported to gain more weight during pregnancy than nonsmokers or smokers (1.3 kg and 0.9 kg average difference, respectively) (Anderson et al. 1984). Rush (1974) reported a reduction in weight gain of 0.12 pounds per week among continuing smokers compared with those who quit. This pattern may reflect the well-established tendency to gain weight following smoking cessation (Manley and Boland 1983; Rabkin 1984), as discussed further in Chapter 11.

There are several hypotheses that attempt to explain the mechanism by which fetal growth is affected by cigarette smoking (Table 1), but cigarette smoking is believed to impact on fetal growth through intrauterine hypoxia (Longo 1977). Carbon monoxide, a component of cigarette smoke, has the ability to cross the placenta and bind with the hemoglobin in both the mother and the fetus producing carboxyhemoglobin. Carboxyhemoglobin reduces the ability of the blood to carry adequate levels of oxygen to the fetus. Smoking is also believed to cause vasoconstriction of the umbilical arteries, and therefore, impact on placental blood flow (Lehtovirta and Forss 1978; Naeye and Tafari 1983; Longo 1982). Cigarette smoking during pregnancy decreases the availability of oxygen to the fetus by both mechanisms.

These mechanisms imply a reversible effect of cigarette smoking for fetal growth because normal function would resume shortly after nicotine or CO is cleared from the system. Support for the suggestion that these effects are reversible is derived from several sources. Davies and coworkers (1979) found that 48 hours of smoking cessation late in pregnancy increased oxygen availability to the fetus. Višnjevac and Mikov (1986) found similarly low levels of carboxyhemoglobin (COHb) in mothers and newborns when the mother was a former smoker or never smoker; mothers who smoked during pregnancy and their newborns had high levels of COHb.

Mechanisms for the effects of smoking on neonatal, perinatal, and infant mortality are poorly understood, although the reduction in birthweight is often considered to be the mediating process. However, smoking appears to cause a shift in the distribution of birthweight without having much effect on mean gestational age (US DHEW 1979; US DHHS 1980), and shifts in birthweight distribution across different populations do not always produce corresponding shifts in mortality (Wilcox 1983; Wilcox and Russell 1983a,b).

That gestational age is little affected by smoking, whereas birthweight is reduced at every gestational age, explains why small infants of smokers have a better prognosis than small infants of nonsmokers (Yerushalmy 1971; MacMahon, Alpert, Salber 1966). Increases in perinatal mortality among smokers may result not from the reduction in birthweight, but rather from the modest increases in preterm delivery, very low birthweight, and specific pathologic conditions such as placenta previa and abruptio placentae. However, this has not been addressed explicitly in any study. Because the smaller smoking-related increases in less frequent, more severe outcomes parallel the pronounced smoking-related reduction in birthweight, birthweight serves as a useful empirical marker of smoking's harmful consequences, even if it is not the direct mediator of those effects.

Nonexperimental Studies

Fertility and Infertility

Consistent evidence indicates that smokers have lower fertility than nonsmokers (Daling et al. 1987; Howe et al. 1985; Baird and Wilcox 1985; Hartz et al. 1987), as noted in the 1989 Report of the Surgeon General (US DHHS 1989). The studies that have assessed indicators of fertility in former smokers are summarized in Table 2.

Pettersson, Fries, and Nillius (1973) studied secondary amenorrhea, one mechanism for reduced fertility, and found an increased prevalence among smokers. However, prevalence among former smokers was even higher than among continuing smokers. Hammond (1961) found that irregular menstrual cycles were more common among smokers than never smokers and that former smokers were at slightly lower risk than never smokers.

Howe and colleagues (1985) analyzed data on more than 4,000 women in a British cohort study, which assessed the safety of oral contraceptives. Compared with never smokers, women who smoked 20 cigarettes or more at entry into the study were twice as likely to be undelivered 5 years after ceasing contraceptive use with the intention of becoming pregnant, whereas former smokers had the same likelihood of being undelivered as never smokers. Baird and Wilcox (1985) reported that the time period until pregnancy was the same for 31 women who quit smoking in the year prior to attempting to conceive as it was for never smokers.

Daling and coworkers (1987) conducted a large case–control study in Washington State and found that, compared with never smokers, the relative risk of primary tubal infertility was 2.7 among current smokers and 1.1 among former smokers. Information

TABLE 2.—Summary of studies of fertility among smokers and former smokers

Reference	Location	Measure of fertility	Relative risk of measure of fertility[a]	
			Smokers	Former smokers
Pettersson, Fries, Nillius (1973)	Sweden	Secondary amenorrhea	1.3	1.6
Howe et al. (1985)	England	Not pregnant 5 yr after ceasing contraceptive use	2.0[b]	1.0
Baird and Wilcox (1985)	Minnesota	Time to pregnancy >1 yr	3.4	1.0
Daling et al. (1987)	Seattle	Primary tubal infertility	2.7	1.0
Daling et al. (1985)	Seattle	Secondary tubal infertility	1.6	1.3

[a]Compared with never smokers.

[b]Smokers of >20 cig/day.

on secondary tubal infertility from the same study (Daling et al. 1985) revealed a smaller difference between current and former smokers. Although the study focused on prior induced abortion, data are presented that allow computation of crude odds ratios for current and former cigarette smokers. Current smokers had a 1.6-fold increase in the risk of secondary tubal infertility, and former smokers had a 1.3-fold increase in risk. It is difficult to assess the causal effect of smoking on tubal infertility independent of the effects of sexually transmitted diseases (STDs) known to co-vary with smoking in many populations.

In summary, the data suggest that impairment of fertility measured as delay in time to conception is related to smoking near the time of attempting to conceive and that smoking cessation prior to conception returns fertility to that of never smokers. Conclusions about smoking and the risk of tubal infertility cannot be drawn because of concern about uncontrolled confounding.

Ectopic Pregnancy and Spontaneous Abortion

Tubal (ectopic) pregnancy occurs at about the same time in the reproductive process as fetal loss. However, the mechanisms are thought to be similar to those operating in tubal infertility and largely concern tubal motility and patency. Several reports indicate an increased risk of ectopic pregnancy in smokers (Campbell and Gray 1987; Matsunaga and Shiota 1980), but only Chow and associates (1988) examined the association with prior smoking in detail. In a case–control study in western Washington State, 155 cases of tubal pregnancy were compared with 456 controls who had given birth. Current smokers had an estimated 2.2-fold increased risk of ectopic pregnancy com-