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The Association of Smoking with Clinical Indicators of Altered Sex Steroids —a Study of 50,145 Women

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Synopsis

This study was designed to test the association of smoking with four clinically apparent conditions that may be related to altered sex steroids: natural and induced menopause, infertility, oligomenorrhea, and hirsutism. Data were obtained from the personal inventories of 50,145 women ages 20-59 years in TOPS, a weight reduction program.

The age-adjusted odds ratios of each condition for heavy smokers compared with nonsmokers were 1.59 for natural menopause, 1.49 for induced menopause, 1.35 for infertility, 1.30 for oligomenorrhea among women younger than 40 years, 1.63 for oligomenorrhea among women 40-49 years, and 1.54 for hirsutism ($P < .05$ for oligomenorrhea and $P < .001$ for all other risks). The odds ratios were not substantially changed after adjustment for obesity, parity, and husband's education level. These results suggest that smoking may affect the ovaries or hormone metabolism, or both, with medical and cosmetic consequences.

HOW SMOKING RELATES to gynecologic abnormalities has been examined in several studies. It has been shown frequently that smoking is associated with natural menopause (*1-6*). Other studies have found smoking to be associated with the inability to become pregnant (*6*), lowered estrogen levels in the luteal phase (*7*), and alterations in the levels of gonadotropins and other hormones that may affect ovarian function (*8*).

One difficulty in evaluating the association of smoking with a given condition is that smokers may differ from nonsmokers in characteristics such as weight (*9,10*) and socioeconomic status (*11*). To isolate the association of smoking with a given

condition, it is necessary to adjust for these characteristics. In this study there were sufficient subjects and sufficient information on each subject to evaluate the association between smoking and clinical indicators of altered sex steroids after adjusting for age, obesity, parity, and husband's education level. The four indicators of altered sex steroids that were investigated are (*a*) natural and induced menopause, (*b*) fertility, (*c*) hirsutism, and (*d*) oligomenorrhea.

Methods

Questionnaires were distributed throughout the United States and Canada in 1969 and 1970 to members of TOPS Club, Inc. (Take Off Pounds Sensibly), a nonprofit organization dedicated to weight reduction. The motivation of the women to participate in a study of obesity was reflected in the thoroughness of their answers on the comprehensive questionnaire. The first part of the two-part questionnaire was completed under the guidance of a leader at a weekly meeting. Each leader was given a protocol for administering the questionnaires. There were 125,000 questionnaires distributed. After excluding women who completed only part of the questionnaire and fewer than 1,000 subjects who were either men or nonwhite women, 72,531 women remained in the study. A further description of the study population and the questionnaire has been published (*12*). In this study we used the 50,145 women between the ages of 20 and 59 years who either currently smoked or had never smoked. Former smokers were excluded because details of their smoking histories were not available.

The subjects were divided into four groups on the basis of the smoking history reported in the questionnaire: women who have never smoked (nonsmokers), women currently smoking 1 to 10 cigarettes per day, women currently smoking 11 to 20 cigarettes per day, and women currently smoking more than 1 pack of cigarettes per day (heavy smokers).

Menopausal status was derived from a woman's answer to the following questions: "Are you still having your monthly menstrual period?" and "Did menopause occur naturally?" Data from 23,310 women between the ages of 40 and 54 years were used to analyze the effect of smoking on menopause. Younger women were excluded because too few were postmenopausal; conversely, older women were excluded because of the low percentage of premenopausal women. Separate analyses were done of smoking as a risk factor for natural menopause and smoking as a risk factor for surgically induced menopause.

Hirsutism was determined by asking "Are there any regions of your body where you consider hair growth to be excessive?" "If yes, where?" Usually only excess hair on the face, chest, abdomen, thighs, or forearm is considered hirsute. According to Segre, "Normal women have little hair in these areas, hirsute women a great deal (*13*)." Excess facial hair is the most visible abnormal hair growth pattern, however, and should be the least subjective indication of virility. For this reason, the only subjects who were considered to be hirsute in this study were women who had excess facial hair. Limiting our definition of hirsutism this way excluded relatively few women who would have been considered hirsute by other criteria. All of the 50,145 women ages 20–59 years were included in the analysis of hirsutism.

Our criterion for infertility was nulliparity that we determined by responses to this question: "Have you ever been pregnant?" To eliminate the reasons for never having been pregnant other than infertility, we included in the study sample only those women who were married and were more than 30 years old in 1969. Also we excluded 183 women who had never been pregnant but who had taken oral contraceptives. Unfortunately, we did not have access to other information concerning the subjects' birth control methods or treatment for infertility. There were 35,973 women included in the analysis of infertility.

Oligomenorrhea was defined in this study as menstrual cycles consistently longer than 36 days. To compare women who had normal menstrual cycles with women who had oligomenorrhea, we excluded women whose menstrual cycles were less than 24 days. The women excluded were more likely to have hormonal irregularities than women with more normal cycles. Women who had taken the birth control pill also were excluded. Because the menstrual cycle of women older than 39 years might have been changed by the approach of menopause, we analyzed data on them separately from those on the younger women. There were 9,000 women ages 20–39 years and 6,601 women ages 40–49 years in the sample used in studying oligomenorrhea.

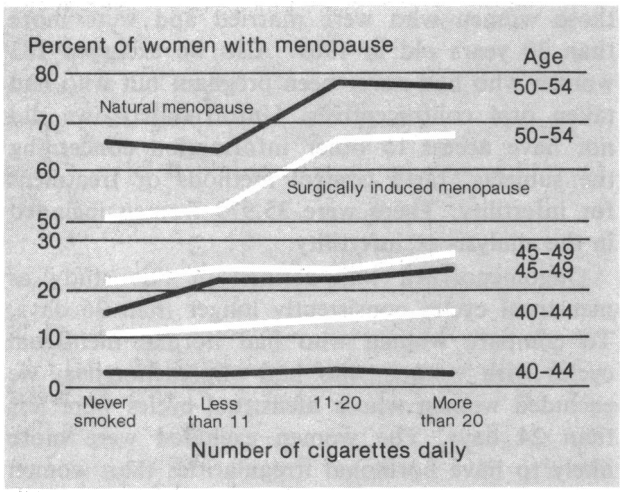
Possible confounding factors considered in the analyses were age, parity, husband's level of education, and relative weight. Relative weight is the percent over the maximum ideal weight for height. To determine ideal body weight, we used

Table 1. Characterization of the study sample of 50,145 women

Category	Percent of women ages 20–39 years (N = 26,994)	Percent of women ages 40–59 years (N = 23, 151)
Parity		
0	9.2	6.6
1	12.2	10.3
2	28.1	25.2
3	23.9	23.8
4 or more	26.6	34.1
Relative weight[1]		
Less than 120	43.5	38.8
121–150	37.3	40.8
151–175	12.8	13.7
More than 175	6.5	6.7
Husband's education (socioeconomic status)		
1–8 years	2.4	8.7
9–12 years	18.9	23.6
High school diploma	48.4	39.8
College and beyond	30.3	27.9

[1] Relative weight = present weight ÷ ideal body weight × 100.

Figure 1. The association of smoking with menopause



NOTE: $P < .001$ except for natural menopause in women ages 40–44 years. Percentages of women with one kind of menopause (natural or surgically induced) were calculated after excluding women with the other type of menopause.

the Metropolitan Life Insurance Tables (*14*) for women of medium build. The subjects' weights were self-reported rather than measured. However, some research suggests that self-reported weights are sufficiently reliable for most studies (*15*).

To test the association of amount smoked with each abnormality, we used the Wilcoxon rank sum test (*16*). We also computed the odds ratio of each abnormality for heavy smokers compared with nonsmokers. The method for computing the odds ratio is illustrated with the use of the following table:

Smoking status	Abnormality: Yes	Abnormality: No
Heavy smoker	*a*	*b*
Nonsmoker	*c*	*d*

The letters *a*, *b*, *c*, and *d* are the number of subjects in each category. The odds ratio *R* is the odds of the abnormality for the heavy smokers ($a \div b$) divided by the odds of the abnormality for the nonsmokers ($c \div d$).

Therefore, $$R = \frac{a \div b}{c \div d} = \frac{a \times d}{b \times c}$$

For highly prevalent conditions, particularly for conditions with a prevalence near one-half, the value of *R* may be considerably higher than the relative risk. For example, if the prevalence of a condition is 50 percent, an odds ratio of 2.7 corresponds to a relative risk of only 1.7. We prefer to use the odds ratio rather than the relative risk since the odds ratio is not affected by the prevalence of a condition in the sample and since mathematical techniques are available to adjust the odds ratio for other variables.

We used the method of Mantel and Haenszel (*17*) to adjust the odds ratio for age in 5-year intervals, parity, relative weight, or education level.

Results

Table 1 characterizes the population studied. The table shows that more than half of the TOPS women met the criterion for obesity (more than 20 percent over ideal body weight). Other studies have shown that TOPS women are less likely to be in the lower or upper socioeconomic groups than the U.S. population as a whole (*12*).

The frequency of both surgically induced and naturally occurring menopause is shown in fig. 1 to increase with the amount smoked in a dose-response relationship. The increase in the rate of natural menopause with smoking is greater for older women. The associations are statistically significant at the $P < .01$ level except for smoking and natural menopause in women ages 40–44. It can be seen from the results in table 2 that the associations are only slightly decreased after adjusting for obesity, parity, or husband's education level.

Shown in fig. 2 is the association between smoking and a history of infertility in married

Table 2: Odds ratios[1] of altered sex steroids associated with heavy smoking and adjusted[2] for 4 confounding factors

Indicators of altered sex steroids and age groups studied	Confounding factors: Age only	Obesity	Parity	Husband's education level	Size of sample
Natural menopause, ages 40–54 years	1.59	1.57	1.52	1.57	11,809
Induced menopause, ages 40–54 years	1.49	1.47	1.42	1.40	11,798
Infertility, ages 30–59 years	1.35	1.33	([3])	1.42	21,557
Oligomenorrhea, ages 20–49 years	1.30	1.28	1.27	1.26	7,084
Virile hair growth, ages 20–59 years	1.54	1.55	1.51	1.57	39,520

[1] All odds ratios are significant at $P < .001$ except those for oligomenorrhea, which have an associated P value of $< .05$.

[2] Adjusted with the use of method of Mantel and Haenszel (*17*).

[3] Infertility cannot be adjusted for parity.

women ages 30–59 years. The infertility is greater for women in their forties than for women in their thirties and much greater for women in their fifties than in the other two groups. This may reflect a number of older women who were not married in their childbearing years or whose childbearing was affected by the Depression and World War II. In all age groups the results suggest that the more the women smoked the more likely they were to be infertile, although the trend is only strong and statistically significant for women more than 50 years old.

Table 2 includes the age-adjusted odds ratio for infertility in heavy smokers after adjusting for obesity and husband's education level. Adjusting for the husband's education level increased the odds ratio slightly. Thus, smoking was not associated with infertility only because of its association with socioeconomic status as measured by the husband's education level.

A strong dose-response relationship of smoking with hirsutism in women older than 30 years is shown in fig. 3. As shown in table 2, adjusting for covariables has no effect on the odds ratios.

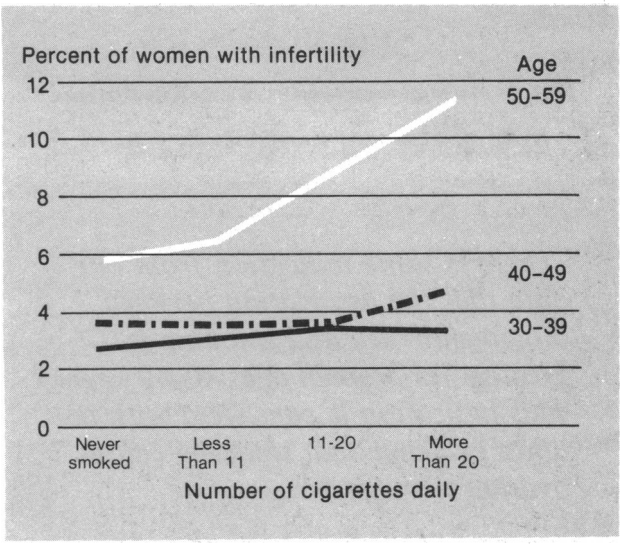
No figure was drawn for women with oligomenorrhea because the number of women with oligomenorrhea in each age group was too small to give meaningful percentages, and pooling women of all ages did not give a dose-response relationship. However, there was a significantly greater risk of oligomenorrhea in heavy smokers than in nonsmokers. This risk was greater for women 40–49 years who were approaching menopause (odds ratio = 1.63) than for younger women (odds ratio = 1.30).

Discussion

This study found that smoking was associated with early menopause (both natural and surgically induced), infertility, hirsutism, and oligomenorrhea. Certain design limitations of the study may have affected the results. These limitations include (*a*) a study population composed primarily of obese women and (*b*) data dependent on a self-administered questionnaire. The first limitation is important only if smoking has a relationship to altered sex steroids among obese women different from that among other groups of women. Previous studies (*1,6*) found, however, odds ratios for the association of smoking with natural menopause and infertility that are similar to the odds ratios found in this study. This suggests that the relationships we found are unlikely to be specific to our population.

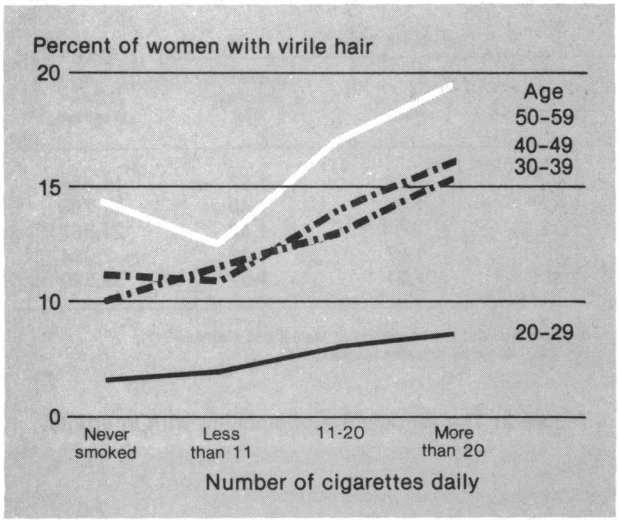
The use of the self-administered questionnaire may have caused us to misclassify women as to the presence or absence of the conditions investigated. For example, women with northern European

Figure 2. The association of smoking with infertility



NOTE: $P < .001$ for age range 50–59 years.

Figure 3. The association of smoking with virile hair growth



NOTE: $P < .01$ at all age ranges except $P < .05$ at age range 20–29 years.

'There is some indication from our data that the association between oligomenorrhea and smoking is greatest for women ages 40–49 years. This indication is consistent with the other evidence that smoking causes ovarian damage.'

ancestory are less likely to notice excess hair growth than women with other ethnic backgrounds. However, errors in questionnaire responses about the conditions investigated in this study are probably unrelated to smoking habits. Rather than lead to spurious associations, these errors will obscure existing associations. Thus, the true effect of smoking may be larger than the effect reported here.

The associations found in this study between smoking and menopause and between smoking and infertility have been reported previously (*1–6*). Our study evaluated these associations after adjusting for potential confounding factors including age, obesity, parity, and socioeconomic status as measured by the husband's education level (*3,18–21*). If smoking affected sex steroids by reducing obesity, adjusting for obesity would tend to obscure the causal chain and artificially decrease the estimated odds ratio. However, adjusting for obesity and the other confounding factors had a negligible effect on the strength of the association between smoking and the conditions investigated. This suggests that the apparent effect of smoking on menopause is not mediated by obesity and is not secondary to the association of smoking with other aspects of lifestyle.

The association of smoking with surgically induced menopause has not been reported previously. Since data on the reasons for surgery were not available in our study, further investigations are needed to identify the particular ovarian or uterine dysfunctions requiring hysterectomy that are most strongly associated with smoking.

The strongest relationship in this study was between hirsutism and smoking, particularly for women ages 30–44 years. Hirsutism is an outward manifestation of altered androgen metabolism. The two sites of potential increased androgen production are the adrenal gland and the ovary. One possible mechanism linking smoking to hirsutism is that smoking is associated with stress, which in turn is associated with polycystic ovary syndrome (*22*)—the most common endocrinopathy causing hirsutism among reproductive-age women.

On the other hand, smoking may directly affect the function of the hypothalamic-pituitary gonadal and adrenal axes. Mattison and Thorgeirsson have suggested that smoking may destroy the oocytes (*23*), leading to increased follicular atresia, hyperplastic theca, and ultimately increased ovarian stroma. The theca and stroma are the sites of androgen production in the ovary. Smoking may enhance estrogen metabolism (*7*), leading to altered estrogen-androgen balance with a predominance of androgenic effects reflected in the target tissue as hirsutism. Smoking may increase luteinizing hormone levels either through a direct pituitary effect or more likely through affecting the catecholamine neuromodulation of the gonadotropin releasing hormone pulse generator. It is also possible that nicotine may contribute to hirsutism by increasing adrenal steroidogenesis (*24*).

All associations discussed previously between smoking and hormonal or ovarian changes may account in part for the association found between smoking and the inability to become pregnant. A common denominator for the abnormalities previously discussed is the polycystic ovary syndrome (*25*), which may be associated with smoking. Other potential mechanisms by which smoking may lead to infertility include the effect of nicotine on the developing zygote (*26*) and on the entry of the

blastocyte into the uterus (*27*). These effects are independent of the effect of smoking on fetal development, which has been extensively studied.

Smoking is probably associated with oligomenorrhea for the same reasons that it is with hirsutism and infertility. There is some indication from our data that the association between oligomenorrhea and smoking is greatest for women ages 40–49 years. This indication is consistent with the other evidence that smoking causes ovarian damage (*23*).

Although cause and effect relationships cannot be proven with epidemiologic studies, there is support for the suggestion that smoking is not only incidentally related but could actually contribute to the alteration of sex steroids. Support for a causal relationship includes the agreement of the results of differently designed studies, the consistent association between smoking and various indicators of altered sex steroids, the minimal effect on our results of adjusting for potential confounding factors, the dose-response relationship, and the supporting theoretical work.

The possible effects of smoking on the ovaries, adrenal glands, and liver are of less medical importance than its effect on the heart and lungs. For some young women, however, heart attacks, emphysema, and lung cancer seem so remote as to be psychologically irrelevant. The fear of hormonal abnormalities may discourage smoking in these women to a greater degree than the fear of more life-threatening but less immediate conditions.

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