Cigarette Smoking and Prematurity

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THERE have been comparatively few controlled studies to determine whether a history of smoking by a gravida, or pregnant woman, increases the risk of having a premature birth. Of the studies that have been done, most have been retrospective in approach, and smoking histories have been obtained post partum. Only two published studies have been prospective.

In the following review prematurity is defined in the various studies as either a birth weight of 2,500 gm. or less or as a birth weight of less than 2,500 gm., unless otherwise indicated.

Retrospective Studies

Review of literature. In 1957 Simpson (*1*) reported that of 7,499 patients delivered in California the incidence of premature birth was nearly twice as great for smoking mothers (11 percent) as for nonsmoking mothers (6 percent). The prematurity rate increased with the number of cigarettes smoked per day. The highest prematurity rate (14 percent) was for heavy smokers, or those who smoked more than 10 cigarettes per day; next highest (9 percent) was for light smokers, or those smoking between 1 and 10 cigarettes per day; and the lowest rate (6 percent) was for nonsmokers.

Lowe (*2*) in 1959 in a similar study of 2,042 women delivered in Birmingham, England, demonstrated that the mean weight of infants of mothers who smoked regularly throughout pregnancy was 170 gm. less than that of infants of mothers who never smoked. Male infants of regular smokers, with a mean birth weight of 3,198 gm., were appreciably lighter than female infants of nonsmokers, with a mean birth weight of 3,279 gm., a reversal of the usual sex difference in weight. There was no substantial difference between duration of gestation for smokers and nonsmokers; that is, for a given birth weight the percentage of mothers who were smokers bore little relation to duration of gestation. For both primiparas and multiparas the infants of smokers weighed less than the infants of nonsmokers. Furthermore, the infants of primiparous nonsmokers, with a mean birth weight of 3,298 gm., were heavier than the infants of multiparous smokers, with a mean birth weight of 3,189 gm. This is contrary to the expectation of heavier newborn among multiparas.

Although in Lowe's study there seemed to be no relationship between smoking and complications of pregnancy, the proportion of pregnancies in which labor was surgically induced was significantly lower among the women who smoked (15 percent) than among those who did not smoke (20 percent), possibly because the size of the fetus is associated with maternal smoking habits. Lowe also found some slight indication that mortality at birth or within

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the first 24 hours among infants of smokers (3.0 percent) was a little higher than among those of nonsmokers (2.3 percent); also that the incidence of major malformations was slightly higher among smokers (1.5 percent) than among nonsmokers (1.1 percent). However, the numbers were too small to permit any definite conclusions. The association of smoking with birth weight was not related to maternal weight, age, and parity.

Villumsen (*3*) reported in 1962 that a few days after their deliveries he had interviewed 1,323 women about their smoking habits in connection with a study of cigarette smoking and prematurity. There was, in general, a rise in the prematurity rate with a rise in the daily consumption of cigarettes by the mothers. He found that 16 percent of infants born to nonsmokers were premature compared with 20 percent of those born to smokers. Women who smoked more than three cigarettes a day during pregnancy had a significantly greater prematurity rate (21.3 percent) than women who smoked three cigarettes or less daily (15.7 percent).

In a study of 2,745 women delivered in Aberdeen, Scotland, Herriot and associates (*4*) reported in 1962 that the prematurity rate was higher for smokers than for nonsmokers in each height-social class grouping. Height was that of the mother. Social class was determined by occupation of the husband—professional or managerial, skilled, semiskilled, or unskilled manual workers. Regardless of gestational age, parity, and sex of infant, the mean birth weight was about 160 gm. lower in babies of smokers than in babies of nonsmokers. There was no clear relationship between the incidence of prematurity and the amount smoked. The authors believed a simple statement that a woman either was or was not a smoker was probably more reliable than one on the amount smoked.

Savel and Roth (*5*) reported a study in 1962 of querying 1,415 private and ward, Negro and white patients on their smoking habits in a Newark hospital immediately following delivery. Patients who smoked even one cigarette a day were considered smokers. A premature birth was one occurring at 36 weeks or less of gestation or where the infant weighed 2,500 gm. or less at birth. For smokers the prematurity rate was 10 percent and for nonsmokers, 6 percent. The average birth weight of babies born to smokers (3,101 gm.) was lower than that for the babies of nonsmokers (3,276 gm.).

Analysis by race showed that for whites the mean birth weight of babies of smoking mothers was 3,141 gm. and for babies of nonsmoking mothers, 3,374 gm. For Negro smokers, the figure was 3,030 gm. and for Negro nonsmokers, 3,173 gm. The prematurity rate for white smokers was 7 percent and for white nonsmokers, 3 percent. The corresponding rates for Negroes were 15 percent and 10 percent.

The average size of babies in the smoking group was inversely related to the number of cigarettes smoked per day. Fetal wastage, stillbirths, and neonatal deaths seemed uninfluenced by the smoking habits of the mother.

In 1963 Zabriskie (*6*) reported a study of 2,000 consecutive single births delivered by 957 smoking and 1,043 nonsmoking gravidas. The smoking history was obtained during the post partum period. Only women who delivered twins were omitted. The following factors were investigated: maternal age, gravidity, parity, abortions, race, weight gain, blood pressure, toxemia, amount and duration of smoking, and sex and weight of the newborn. A smoker was one who smoked regularly each day.

Zabriskie found that women who smoked had infants with a mean birth weight of 3,091 gm., an average of 229 gm. less than those of nonsmokers, whose infants had a mean birth weight of 3,320 gm. The prematurity rate among infants born to smokers (9.93 percent) was 2½ times higher than among infants born to nonsmokers (3.83 percent). Women who smoked gave a history of having aborted relatively more frequently than nonsmokers (12.6 percent versus 8.8 percent of all pregnancies) and the abortion rate appeared to increase with the amount smoked. No appreciable difference was found in age, parity, blood pressure, pulse rate, weight gain, or incidence of toxemia between smokers and nonsmokers.

O'Lane (*7*) in 1963 reported a study of the smoking habits of 1,031 Caucasian women who had single vaginal deliveries. The patients, smokers and nonsmokers, were unselected, being picked for the study in the order in which they

delivered. Women who started or stopped smoking during their pregnancies were excluded, as were women whose babies weighed less than 500 gm. The required information was recorded at the time of delivery. The patient's history was obtained from the prenatal records and from direct questioning in the hospital.

The smoking and nonsmoking groups were evaluated in regard to certain parameters to determine if the groups were statistically comparable. No significant statistical differences were found in age, prenatal care, complications of previous pregnancies, complications of the current pregnancy, including toxemia, ante partum concentration of hemoglobin, blood types, and Rh distribution. Apgar ratings consisting of more or less subjective ratings of the neonatal heart rate, respiratory effort, muscle tone, reflex irritability, and color which could range from a high of 10 for the least distressed infant to 0 for the most distressed, as well as data on fetal length, fetal weight, and placental weight, were recorded promptly after delivery.

The group consisted of 566 nonsmokers and 465 smokers. Women were classed as smokers if they regularly smoked each day. Smokers who did not smoke daily were excluded from the study. Those classified as nonsmokers did not smoke at all during pregnancy. Because of the relatively small numbers in some of the smoking-consumption groups, it was decided to treat all smokers as one group regardless of amount smoked.

The smoking mothers produced infants that were lighter (mean birth weight 2,938 gm.) and shorter (mean fetal crown-heel length 19.8 inches) than those of nonsmoking mothers (mean birth weight 2,978 gm. and mean fetal crown-heel length 20.3 inches). The difference in fetal length was statistically significant. The prematurity rate for the smoking mothers (11.8 percent) was more than twice that for the nonsmoking group (5.1 percent). This difference was statistically significant. The smoking group had significantly more abortions in all prior pregnancies (12.6 percent) than did the nonsmokers (8.9 percent). The Apgar scores of the smokers' babies were significantly lower (8.18) than those of the nonsmokers' babies (8.63). There were no significant differences for the two groups in the mean initial weights, maternal weight gain, placental weights, fetal and perinatal death rates, or length of gestation.

Discussion. In all the retrospective studies the data were gathered after the birth of the child, which meant that the mother knew if the child was premature when she was questioned by the interviewer regarding her smoking habits. To what extent this influenced her replies is not known, although replies might be biased by knowledge of the outcome. Furthermore, the information elicited from the mother might be clouded by loss of memory or distortion.

In Simpson's study (*1*) there is the added possibility of bias as a result of the way the study was conducted. When a baby was premature, a public health nurse visited the home and queried the mother about her smoking habits. This additional querying resulted in reclassification of some women from nonsmoker to smoker. However, no such additional queries were made if the baby was not premature. None of these studies considered the duration of smoking. Only Lowe (*2*) considered whether the smoking had started before or during the pregnancy. In the O'Lane study (*7*) the smokers were limited to those smoking before and throughout the pregnancy, while nonsmokers were those who had never smoked.

O'Lane found a significant mean reduction in Apgar scores for infants of the smoking group. Data on the significance of any decreases in the five components of the Apgar score would be of great interest.

Prospective Studies

Review of literature. The first published prospective study of cigarette smoking and prematurity was reported in 1961 by Frazier and associates (*8*). This study was jointly conducted by the Baltimore City Health Department and the Biometrics Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health. Available through the operations of the prenatal clinic of the Baltimore City Health Department were (*a*) a racially and economically homogeneous population, (*b*) uniform prenatal and obstetrical facilities, and (*c*) a mechanism for follow-

ing all deliveries, the vital records system. A simplified questionnaire was precisely designed to meet the objectives of the study. All subjects in the study were interviewed initially in the maternity interviewing clinic of the department so that variation in procedure was reduced to a minimum and data could be reliably and uniformly collected. A woman was classified as a smoker if she smoked every day. All others, the nonsmoker and the occasional smoker, were classified as nonsmokers.

This study of 2,736 Negro gravidas, delivered of single live born infants at the Baltimore City Hospital, showed a difference of 156 gm. between mean birth weights of infants of smokers at 2,924 gm. and infants of nonsmokers at 3,080 gm. The prematurity rate for smokers was 18.4 percent and for nonsmokers, 11.2 percent. These rates can be compared with 11.0 percent observed for those women who elected to stop smoking during the pregnancy and before the time of the interview.

A comparison of smoking history before pregnancy and at the time of the interview showed consistency in smoking patterns. The prematurity rate increased with the amount smoked during pregnancy. The difference in prematurity rates of smokers and nonsmokers was independent of maternal age, blood group type, initial hemoglobin level, sex of child, work history, education, and psychosomatic complaint score.

Although a difference in the prematurity rate for smokers and nonsmokers was found for the 2,234 multigravidas in this study, it was not found to be significant for the 502 primigravidas. However, it should be noted that of the primigravidous smokers only 31 percent smoked more than half a pack per day compared with 41 percent of the multigravidous smokers. The lack of a significant difference among the primigravidas is perhaps related to the fact that in this group there were proportionately fewer heavy smokers than among the multigravidas. Also, it is possible that the effect of primigravidity, which tends to increase the rate of prematurity, is greater than the association of prematurity with smoking per se, thereby accounting for a diminished difference between nonsmokers and smokers. While both fetal and neonatal death rates were higher for infants of smokers than for infants of nonsmokers, only the fetal death rate difference was significant.

Yerushalmy (*9*) in 1960 reported preliminary findings on the outcome of 982 pregnancies in a study of the relationship of factors in parents to the development of their infants. In the course of this investigation, information was obtained on cigarette smoking habits and other characteristics of the husband and wife during the wife's pregnancy and before the birth of the infant. The information on smoking habits was obtained by interviewing the mother. The smoking habits of the father at the initial stages of the investigation were obtained by means of a special form which the gravida took home for her husband to complete. In the later stages, information about the husband's smoking habits was obtained directly from the gravida. Premature births were defined as birth weights under 5 pounds 8 ounces (2,495 gm.).

An association was reported between the smoking habits of the mother and the birth weight of her infant. For smoking mothers the prematurity rate was 8.1 percent and for nonsmoking mothers, 5.9 percent. There was no significant difference between mothers who smoked less than one pack of cigarettes daily and had a prematurity rate of 8.0 percent and those smoking one or more packs daily and having a prematurity rate of 8.1 percent. Similarly, past smokers, or those who no longer smoked, had a prematurity rate of 5.9 percent, almost identical to that of mothers who never smoked, at 6.0 percent.

Findings for the fathers were quite similar, except that there was a more definite relationship between amount smoked daily by them and the prematurity rate for their wives. For instance, the prematurity rate for wives of smoking husbands was 7.8 percent and for nonsmoking husbands, 5.4 percent. Husbands smoking one pack daily had wives with a prematurity rate of 6.7 percent, one to two packs daily, 8.4 percent, and two or more packs daily, 10.8 percent. There was almost no difference between the prematurity rates of wives of past smokers (5.3 percent) and nonsmokers (5.5 percent). Yerushalmy's position is that smoking by the father is a condition which a priori would not be expected to be causally related to prematurity in his wife's infants. Hence, finding such

a so-called "nonsense" relationship, according to him, weakens support for the belief that the relationship between smoking in the mother and prematurity in the infant is causal.

Yerushalmy also presented data on the association between birth weight of infant and smoking habits of both father and mother. For instance, in the smoking habits of 982 sets of parents, both parents were smokers in 267 sets and the prematurity rate was 9.4 percent, only the husband smoked in 256 sets and the prematurity rate was 6.2 percent, only the wife smoked in 109 sets and the prematurity rate was 4.6 percent, and in 350 sets neither parent smoked and the prematurity rate was 5.7 percent. The prematurity rate when both parents smoked was significantly greater than the prematurity rates for the remaining three categories in which only one or neither parent smoked.

Yerushalmy also found that if at least one parent did not smoke, or if neither of them smoked, the prematurity rates were approximately the same. He had no explanation for this on a causal basis but indicated that in the study by Frazier and associates (*8*), where the joint effect of two variables on prematurity, smoking by the mother and her psychosomatic complaint score, was studied, a similar situation was found. If the mother was a smoker and also attained a critical (high) psychosomatic complaint score, they found that the prematurity rate was greatly increased.

Yerushalmy explained the findings on the basis that smoking acts as an index to differentiate smokers from nonsmokers on a number of different characteristics rather than as indicating a causal relationship. This stems mainly from the fact that smokers and nonsmokers have self-selected themselves into noncomparable groups, in the opinion of the investigator.

Preliminary unpublished findings were made available to us in January 1963 through Dr. H. Berendes, chief, Perinatal Research Branch, regarding the perinatal collaborative study sponsored and coordinated by the National Institute of Neurological Diseases and Blindness, National Institutes of Health. The data concerned the relationship between smoking and birth weight as determined from a study of 7,018 pregnancies terminating in single live births.

Smoking histories were obtained at the time of registration for prenatal care in 10 cooperating hospitals throughout the country. Smokers were defined as women who were smoking at the time of registration and had smoked at least five packs of cigarettes during their lives. It was found that among smokers there was a significantly higher prematurity rate (11.3 percent) than among nonsmokers (7.7 percent). This relationship was true for each racial group. The prematurity rate for white smokers was 8.7 percent, for white nonsmokers 5.1 percent, for Negro smokers 14.4 percent, for Negro nonsmokers 10.4 percent, for smokers of other races 11.5 percent, and for nonsmokers of other races 4.9 percent.

Discussion. All the evidence, whether obtained from retrospective or prospective studies, points to an association between smoking and prematurity. The consistency of results, whether based on retrospective or prospective studies, leads one to believe that the usual arguments about the possible bias of retrospective studies do not apply here. The association tends to retard fetal growth but not by shortening gestation as a result of earlier onset of labor. Some studies have shown that from approximately the 34th week of gestation the mean birth weight of infants of nonsmokers was consistently greater than the mean birth weight of infants of smokers.

Most studies appear to indicate a direct correlation between prematurity rate and the amount smoked. This may be construed as an argument for causation. If there is truly a causal relationship, a number of explanations come to mind.

1. Smoking may reduce maternal appetite to the extent that it would manifest itself in reduced weight of the newborn infant.

2. Vasoconstriction caused by smoking might have an appreciable effect on fetal nutrition through a decrease in the blood supply reaching the intervillous space, thus reducing the supply of nutritive substances and causing a lag in the removal of catabolites; Herriot and associates (*4*) would approach a mechanistic explanation through a study of the placental transfer of labeled nutrients in smokers and nonsmokers, as well as in a comparison of oxygen levels in cord blood.

3. Smoking may have a direct toxic effect on fetal metabolism.

4. Smoking elevates the blood carbon monoxide concentration in the mother and, consequently, in the blood reaching the fetus (*10*). Carbon monoxide in high concentrations reduces the oxygen-carrying capacity of the blood and acts as a teratogenic agent to increase the risk of fetal death and maldevelopment.

In any explanation of the observed association between smoking and prematurity one must be on the alert for possible third factors or for a multiplicity of causes related both to smoking habits and reduced birth weight. For instance, in the Simpson study (*1*) data were collected from a county hospital and two private hospitals. The prematurity rate for nonsmokers in the county hospital exceeded that in the two private hospitals, possibly because of the influence of socioeconomic factors.

Yerushalmy (*9*) has indicated that while the association between cigarette smoking and prematurity may indicate a cause-effect relationship, it may also be due to differences between smokers and nonsmokers in characteristics other than smoking. To establish and evaluate the specificity of the association observed between smoking gravidas and prematurity, he attempted to determine whether there was an association between a condition which a priori would not be expected to be causally related to prematurity in the infant and the incidence of prematurity.

It appeared to Yerushalmy that the smoking habit of the father might serve the desired purpose, for it could not reasonably be expected to be related to birth weight of the infant. However, there is evidence of a definite relationship between smoking habits of husbands and wives. Analysis of unpublished data from W. Haenszel, chief, Biometry Branch, National Cancer Institute, on tobacco smoking habits in the United States showed that when wives were classified as nonsmokers, occasional smokers, and regular smokers, there was a corresponding increase in the percentage of husbands who were regular smokers. Furthermore, classifying wives who were regular smokers by amount smoked daily (under 10 cigarettes, 10 to 20 cigarettes, and 21 or more cigarettes) again showed a correspondingly greater percentage of husbands who were regular smokers. Finally, the data showed that an increase in the daily consumption of cigarettes by wives was accompanied by a corresponding increase in the mean daily consumption of cigarettes by their husbands. The above associations held when data were analyzed separately for husbands under 45 years of age as well as for those 45 years and over. It is presumed that similar relationships hold for pregnant women.

Since smoking habits of the husband are definitely related to smoking habits of the wife, it follows that an association between cigarette smoking by the gravida and prematurity would result in a similar association between the father's smoking habits and prematurity. Furthermore, it is not inconceivable that paternal smoking could alter the paternal germ plasm and have an identifiable effect on the fetus. Hence, the use of father's smoking habits is questionable as a nonsense variable by which to establish specificity of the association between smoking gravidas and prematurity.

Yerushalmy's data on smoking habits of both parents in relation to prematurity are not clear cut. For example, in view of the apparent association between smoking habits of spouses, one might consider smoking by fathers as a nonsense variable only when the mother is a nonsmoker. In Yerushalmy's data, although based on small numbers, the difference in prematurity rates between smoking fathers and nonsmoking fathers, independent of mother's smoking habits, was not significant. When Yerushalmy computed the percentage of premature infants born to parents where both smoke (9.4 percent) with the percentage where both do not smoke (5.7 percent), he found statistical significance. However, since this comparison confounds the effect of smoking habits of the mother, it is irrelevant to an investigation into the effect of father's smoking habits when mother's smoking is held constant. Yerushalmy's data do not show any significant linear dependence of prematurity on amounts smoked by the father. In summary, his data failed to establish any association between birth weight and the father's smoking habits independent of the mother's smoking habits.

While the prospective approach remedies the difficulties inherent in retrospective studies

with respect to obtaining data for correlation with an event (for example, premature birth) after that event is known, there are still other problems that need solution if definite statements of causality are to stand up. It is possible, of course, that the type of gravida who smokes is, by virtue of other characteristics, the type that would have a premature birth whether she smoked or not. In other words, it is possible that the smoking gravida population, in whole or in part, is to some degree self-selected. If this is so, then any type of epidemiologic observation, retrospective or prospective, would be plagued by this difficulty.

An approach to a solution would lie in a clinically controlled study of smoking gravidas, randomized into two groups, one serving as a control and the other as an experimental group. The experimental variable would be the cessation of smoking during pregnancy and the criterion of the effect would be the prematurity rate. A major difficulty to be surmounted would be to devise an effective method of getting women to discontinue smoking. In addition, it would be necessary to develop an objective method of determining the validity of smoking histories given by women subjected to discontinuance of smoking to confirm the fact that when a woman claims to have stopped smoking she has, in fact, stopped smoking.

It would also be well to obtain prematurity, stillbirth, and neonatal death histories for all previous pregnancies of women in the study so that appropriate rates, based on pregnancies, could be computed for each group. It might also be possible to use a woman as her own control and compare outcomes when she smoked with those when she did not smoke, giving consideration to the effect of gravidity on outcome. However, reliable data on prior smoking history and birth weights of previous pregnancies might be difficult to obtain.

Needed Research

The argument for causation can be tested by comparing outcomes for women who were motivated to stop smoking during pregnancy with the outcomes for a similar population who were not so motivated. It is not known to what extent the woman who stops smoking after being motivated to do so differs from the woman who stops voluntarily. However, the relationship of smoking and prematurity for each of these groups of women can be evaluated separately with proper study design. As noted earlier, one must bear in mind the possibility of a multiplicity of causes related to smoking habits and reduced birth weight.

The Southwest Research Institute in San Antonio recently reported a possible approach to developing an objective method of assessing the fact of smoking as well as, roughly, the amount smoked by determining through gas chromatography methods the acetonitrile in the urine (*11*). To utilize this approach in connection with future studies, the Biometrics Branch of the National Institute of Neurological Diseases and Blindness, with the cooperation of the Southwest Research Institute, has determined for women (*a*) the association between cigarette smoking and the detection of acetonitrile in the urine, (*b*) the quantitative relationship between amount smoked and the level of acetonitrile, (*c*) the time lag between change in smoking habits and change in acetonitrile content, and (*d*) the effect, if any, of food on the ability to detect the presence and to measure the level of acetonitrile in the urine. Subsequently, a faster colorimetric method was developed for detecting acetonitrile, correlating highly with the gas chromatographic method.

If found feasible, the relationship between acetonitrile and smoking could be used in a clinical trial of the association between cigarette smoking and prematurity as a means of substantiating all statements regarding the cessation or reduction of smoking. The Biometrics Branch, National Institute of Neurological Diseases and Blindness, has sponsored the development of methodology by which it may be possible to conduct a clinical trial to compare outcomes for women motivated to stop or reduce smoking during pregnancy with a comparable population not so motivated. The outcomes, including the rate of prematurity, for these women as well as those voluntarily stopping the smoking habit could be studied. The fact of smoking or nonsmoking could be established by the acetonitrile data. A first step in the project would be determining the degree of success that various motivational techniques

would have in getting women to stop or reduce smoking during the remainder of their pregnancy. A thorny problem that may still remain is the possible self-selection of those women who continue smoking despite the motivation to stop. Should such a situation develop, this group would be evaluated separately. However, it may not be possible to determine whether such women would have had the same outcomes whether or not they stopped smoking.

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Lung Cancer Deaths in Women

Female smokers showed a lung cancer death rate of 101.4 per 100,000 population in a Public Health Service study of a 10 percent sample of white women over 35 years of age who died of lung cancer during 1958–59. Earlier data for male smokers had established a lung cancer death rate of 392.8.

The study revealed that for female nonsmokers the lung cancer death rate is 9.4 compared with 12.5 for male nonsmokers, a difference by sex in line with that for most causes of death.

Lung cancer findings for women agree in general with the earlier ones for men. The more women smoke, the greater their chance of developing lung cancer; the risk is greatest for heavy smokers who move frequently and for the foreign-born settling in large cities.

These and other findings were obtained in a survey of lung cancer mortality as related to residence and smoking histories conducted by Public Health Service scientists and reported in the April 1964 issue of the *Journal of the National Cancer Institute.* (The study on white males appeared in the April 1962 issue of that journal.) National Cancer Institute researchers collected from relatives the data on the residence and smoking histories of the 683 women in the sample.