

PAPERS AND ORIGINALS

Cigarette Smoking in Pregnancy: Its Influence on Birth Weight and Perinatal Mortality

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British Medical Journal, 1972, 2, 127-130

Summary

In a British population cigarette smoking during pregnancy increased the late fetal plus neonatal mortality rate by 28% and reduced birth weight by 170 g, and these differences persist even after allowing for a number of "mediating" maternal and social variables. A change in smoking habit by the end of the fourth month of pregnancy places a mother in the risk category appropriate to her changed habit. This evidence should have important implications for health education aimed at getting pregnant mothers to give up smoking.

Introduction

Simpson (1957) was the first to report a lowering of birth weight among the offspring of mothers who smoked during pregnancy. A number of subsequent studies, reviewed by Roberts (1969), have confirmed this effect, showing a mean reduction in birth weight varying between 150 and 250 g. A small reduction in mean duration of pregnancy of up to three days has also been reported. It is also reasonable to expect that since there is a lowering of mean birth weight there should be an increase in perinatal mortality. In the 1958 British Perinatal Mortality Survey (Butler and Alberman, 1969) birth weight was reduced by 170 g in the offspring of smokers, with a corresponding rise in late fetal and neonatal mortality, the excess of deaths being mainly accounted for at necropsy by causes associated with low birth weight. Mothers who smoked in pregnancy tended to come from poorer social backgrounds, were older, and were of higher parity than non-smokers. This raised the possibility that smoking "caused" neither the lowering of birth weight nor the increase in perinatal mortality, but was rather an index of a particular type of mother, a viewpoint advanced by Yerushalmy (1964).

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Butler and Alberman (1969) attempted to overcome this objection by making allowance statistically for a number of other possible "mediating" variables such as social class, maternal age, parity, and height, and showed that the differences in birth weight and perinatal mortality between smokers and non-smokers remained. The effect of smoking in pregnancy was also found to persist into later life. Over 90% of the surviving British children were re-examined at 7 years of age and the children of mothers who had smoked in pregnancy were found to be on average shorter than those of non-smoking mothers and to suffer some educational retardation. These findings again persisted after allowing for a number of mediating factors (Goldstein, 1971; Davie *et al.*, 1972).

The purpose of the present paper is to extend the analyses previously reported from the British Perinatal Mortality Survey. Whereas mothers were previously categorized simply as either smokers or non-smokers, the smokers are now divided into four groups, based on the average number of cigarettes smoked. The analysis also considers the effect of change in number smoked between the beginning of pregnancy and the end of the fourth month. If smoking itself (rather than the type of woman who smokes) has a deleterious effect on the fetus, it would be reasonable to expect the mothers who gave up smoking during pregnancy to show differences in the birth weight and perinatal mortality of their offspring compared with those who continued to smoke.

Method

The British Perinatal Mortality Survey of the National Birthday Trust Fund (Butler and Bonham, 1963; Butler and Alberman, 1969) collected perinatal data relating to 16,994 singleton births in England, Scotland, and Wales during the week of 3-9 March 1958 and on nearly 7,000 late fetal and neonatal deaths occurring during the following three months of March, April, and May 1958. The survey included 98% of all births registered during the week and 95% of the deaths during the three months. As the smoking habits and sociobiological and obstetric profile of mothers of the babies dying among the week's births did not differ from those of the three months' deaths, all the deaths have been aggregated for statistical purposes.

The information on smoking was obtained as a special item in a questionnaire completed by midwives at the time of the delivery or shortly afterwards. The mother was asked how

many cigarettes (if any) she had usually smoked daily during the 12 months before the start of the current pregnancy and how many she had smoked during this pregnancy. Where any change was reported in the number smoked during pregnancy the information was obtained on the month(s) at which such change(s) took place, and the number smoked after the change. However, only their regular smoking habits before the start of pregnancy and after the end of the fourth month were coded. The choice of these intervals allowed an appraisal of the effect of changes of smoking during the first half of pregnancy, and also an evaluation of the effect of regular smoking during the latter half of the pregnancy when the maximum increase in fetal weight would be expected to take place.

Results

LATE FETAL AND NEONATAL MORTALITY

Table I (a) shows the late fetal rates and Table I (b) the neonatal mortality rates according to whether, subsequent to the end of the fourth month of pregnancy, the mother was a non-smoker

TABLE I—Late Fetal and Neonatal Mortality by Smoking after 4th Month of Pregnancy

	Smoker	Non-smoker	Total
(a) Stillbirths			
Late fetal death ..	1,492	2,486	3,978
Livebirth	5,398	12,412	17,810
Total births	6,890	14,898	21,788
Estimated* late fetal rate	25.2	19.4	21.2

Mortality ratio = 1.30. χ^2 (1 D.F.) = 77.6. $P < 0.001$.

	Smoker	Non-smoker	Total
(b) Neonatal Deaths			
Neonatal deaths	947	1,628	2,575
Survivors + late fetal deaths	5,943	13,270	19,213
Total births	6,890	14,898	21,788
Estimated* neonatal death rate (all births)	15.9	12.6	13.7
Estimated neonatal death rate (live births)†	17.6	13.7	14.9

Mortality ratio = 1.26. χ^2 (1 D.F.) = 35.6. $P < 0.001$.

	Smoker	Non-smoker	Total
(c) Late Fetal and Neonatal Deaths			
Late fetal and neonatal death	2,439	4,114	6,553
Survivor	4,451	10,784	15,235
Total births	6,890	14,898	21,788
Estimated* death rate	41.1	32.0	34.9

Mortality ratio = 1.28. χ^2 (1 D.F.) = 135.4. $P < 0.001$.

*The mean late fetal plus neonatal death rate in the "main week" sample (3-9 March 1958) is 34.9 per 1,000 births. A correction factor of 0.116 is used to adjust the rates obtained when the three-months deaths are included, so that the mean stillbirth plus neonatal death rate is the same as that for the main week.

†The mean neonatal death rate in the main week, using the number of livebirths as denominator, is 14.9 per 1,000. A correction factor of 0.118 is used to adjust the three-months neonatal death rate, so that the mean neonatal death rate is the same as that for the main week.

or a steady smoker with no reported change in average daily consumption. There is a statistically highly significant association both for late fetal and neonatal deaths, the increase in late fetal rate being 30% and in neonatal death rate being 26%. Since the death rate per 1,000 births for smokers divided by that for non-smokers (mortality ratio) for late fetal is similar to the mortality ratio for neonatal deaths (1.30 and 1.26 respectively) we have combined these in all subsequent analyses of mortality and this has the advantage of providing larger numbers for analysis. The mortality ratio for late fetal plus neonatal deaths is seen to be 1.28.

Tables II (a) and (b) indicate the mortality rate for late fetal plus neonatal deaths according to the average number of cigarettes smoked per day before the start of pregnancy and after the end of the fourth month respectively. On both occa-

TABLE II—Late Fetal and Neonatal Deaths according to Number of Cigarettes Smoked Daily (Percentages in Parentheses)

	Average No. of Cigarettes Daily					Total
	0	1-4	5-9	10-19	20-30	
Survivors	9,633 (63.5)	1,112 (7.3)	1,875 (12.4)	2,243 (14.8)	305 (2.0)	15,168 (100)
Late Fetal and neonatal deaths ..	3,697 (56.8)	512 (7.9)	977 (15.0)	1,135 (17.5)	182 (2.8)	6,503 (100)
Total births	13,330 (61.5)	1,624 (7.5)	2,852 (13.2)	3,378 (15.6)	487 (2.2)	21,671 (100)
Estimated* death rate	32.1	36.5	39.8	39.0	43.4	34.8

Test for association: χ^2 (4 D.F.) = 92.4. $P < 0.001$.

	Average No. of Cigarettes Daily					Total
	0	1-4	5-9	10-19	20-30	
Survivors	10,767 (71.0)	1,101 (7.3)	1,397 (9.2)	1,641 (10.8)	262 (1.7)	15,168 (100)
Late Fetal and neonatal deaths ..	4,099 (63.0)	547 (8.4)	797 (12.3)	916 (14.1)	144 (2.2)	6,503 (100)
Total births	14,866 (68.5)	1,648 (7.6)	2,194 (10.1)	2,557 (11.9)	406 (1.9)	21,671 (100)
Estimated* death rate	32.0	38.5	42.2	41.6	41.2	34.8

Test for association: χ^2 (4 D.F.) = 138.6. $P < 0.001$.

(c) Joint Effects of Smoking before and after 4th month of pregnancy, on late fetal and neonatal death rate

An analysis of variance was carried out, using a main effects model with a logit transformation of the dependent variable (see Butler and Alberman (1969) for a justification of this model). The two independent variables are the number of cigarettes smoked before pregnancy and after the fourth month of pregnancy, each in five groups. The dependent variable is the proportion of late fetal and neonatal deaths. The following gives the death rates estimated by using this main effects model.

	Estimated* death rates					
	Cigarettes smoked after 4th month of pregnancy	Cigarettes smoked before pregnancy				
		0	1-4	5-9	10-19	20-30
0	32.2	31.7	31.1	28.1	35.2	32.0
1-4	39.8	39.2	38.5	35.0	43.1	38.5
5-9	44.2	43.5	42.8	39.2	47.6	42.2
10-19	46.6	45.7	44.9	41.2	49.8	41.6
20-30	40.0	39.3	38.6	35.3	43.3	41.2
Total	32.1	36.5	39.8	39.0	43.4	34.8

Significance tests (χ^2 values are adjusted for the other factor):

Smoking before pregnancy χ^2 (4 D.F.) = 9.2. $P > 0.05$.

Smoking after 4th month of pregnancy χ^2 (4 D.F.) = 53.9. $P < 0.001$.

"Goodness of fit" of model χ^2 (16 D.F.) = 11.8. $P > 0.05$.

*See Table I.

N.B. The slightly different totals in this table compared with Table I are due to the fact that this table excludes those smoking over 30 a day before or after the 4th month of pregnancy.

sions the death rate was lowest where the mother was a non-smoker, intermediate in those smoking one to four cigarettes daily, and highest in those smoking over four cigarettes daily. It can also be seen that the percentage of mothers in each group changes, the proportion of non-smokers increasing from 61.5% before pregnancy to 68.5% after the end of the fourth month. This change in smoking habits among a large number of women enabled an analysis of the effect of a change in habits to be carried out.

Table II (c) shows that the average number of cigarettes smoked per day before pregnancy does not significantly influence fetal survival when account is taken of the average number smoked regularly after the fourth month of pregnancy. Thus it seems that smoking habits established at the end of the fourth month of pregnancy have an effect on perinatal mortality which is independent of the mother's pre-pregnancy smoking habits.

BIRTH WEIGHT

In the full statistical analysis allowance is made for a number of maternal variables which might "mediate" the smoking and

birth weight relationship. These are: social class, maternal age, parity, and maternal height. In addition, allowance is made for sex, gestational maturity in completed weeks, and perinatal mortality, since these fetal variables account for a large amount of the variation in birth weight. The results of this analysis are very similar to the analysis made without allowing for these variables, and for simplicity only the results of the latter analysis are presented in Table III. This shows the effects on birth weight of the average number of cigarettes smoked before pregnancy and after the fourth month. It can be seen that the mean birth weight decreases from 3,386 g when no cigarettes are smoked after the fourth month to 3,175 g when 20-30 are smoked, and there is a similar decrease according to the number smoked before pregnancy. As with mortality, the effect on birth weight of smoking before pregnancy becomes non-significant after taking into account the average number smoked regularly after the fourth month.

TABLE III—Relation of Birth Weight to Smoking before Pregnancy and after 4th Month of Pregnancy

An analysis of variance was carried out, on the main week population only, using a "main effects" model with birth weight as dependent variable. The two independent variables—smoking before pregnancy and smoking after the 4th month of pregnancy—were used and constants were also fitted for the following "mediating" variables, which are associated with birth weight or smoking or with both: (a) sex, (b) mortality (survivor or death), (c) social class (Registrar General I + II, III, IV + V), (d) maternal age ≤ 20 , 21-24, 25-34, ≥ 35 , (e) maternal height (in cm), (f) parity (0, 1, 2-3, ≥ 4), (g) gestation (≤ 36 , 37, 38, 39, 40, 41, ≥ 42). Significance tests (the χ^2 statistic is used since the denominator degrees of freedom of the F statistic are large): Smoking before pregnancy (fitting constants for mediating variables and smoking after 4th month) χ^2 (4 D.F.) = 2.4. $P > 0.05$. Smoking after 4th month of pregnancy (fitting constants for mediating variables and smoking before) χ^2 (4 D.F.) = 85.5. $P < 0.001$. The following table gives mean birth weights by smoking categories, estimated by using a main effects model without the mediating variables. (The constants for smoking are similar whether or not the constants for the mediating variables are fitted.)

		Estimated Birth Weight (g)					
		Cigarettes smoked before pregnancy					
		0	1-4	5-9	10-19	20-30	Total
Cigarettes smoked after 4th month of pregnancy	0	3,387	3,382	3,392	3,392	3,355	3,386
	1-4	3,298	3,293	3,303	3,303	3,266	3,295
	5-9	3,202	3,197	3,207	3,207	3,170	3,204
	10-19	3,206	3,201	3,211	3,211	3,174	3,208
	20-30	3,211	3,206	3,216	3,216	3,179	3,175
	Total	3,386	3,325	3,262	3,236	3,188	3,340

Discussion

Before discussing the implications of the above results we must take note of the conflicting published evidence on the relation between smoking in pregnancy and infant loss in the fetal or neonatal period. Two large-scale studies (Underwood *et al.*, 1969; Rantakallio, 1969), in U.S. Naval wives and in Finnish women respectively, showed very small and non-significant differences in perinatal mortality between smokers and non-smokers. Similarly, Yerushalmy (1971), in a study of white American mothers, showed only a very small difference in neonatal mortality rates.

On the other hand, among American Negroes, Frazier *et al.* (1961) found a significantly higher late fetal death rate among smokers. The neonatal death rate was also higher in the same study and also in Yerushalmy's (1971) study of Negro mothers though neither reached statistical significance.

In these latter two studies the neonatal mortality ratio was 1.17 and 1.26 compared with 1.26 for the present study in a large representative British population in which the smokers have a significantly higher neonatal death rate (see Table I). It seems possible that the two U.S.A. studies in Negro populations fail to show statistical significance because of the relatively small numbers involved, about 3,000 births in each case.

The adequacy of the sample size is of great importance in mortality studies of this type. Cornfield and Haenszel (1960)

and others have pointed out that, in the study of diseases with small incidences, a retrospective investigation may have a considerable advantage in that it can study a large number of "diseased" individuals (in this case late fetal and neonatal deaths) and controls, as opposed to the need to study a very much larger population prospectively to yield a similar number of diseased cases. The present study not only contains the 16,994 births from one week but also nearly 7,000 deaths, so that in relation to the sensitivity involved in the comparison of death rates this sample is equivalent to a prospective sample of births many times larger. In fact, in terms of the comparison of late fetal plus neonatal mortality rates between smokers and non-smokers, this sample is equivalent to about 150,000 births. As such it is larger than all the other major studies put together. It should also be pointed out that though the present study is retrospective in that pregnancy smoking habits were inquired into at the time of the child's birth, it is unlikely that a bias was introduced thereby, since at the time of the inquiry there had been no publicity concerning the effects of smoking in pregnancy.

If one assumes the same late fetal and neonatal mortality rates for smokers and non-smokers as were found in the present study, a sample size of about 23,000 births would be required in order to have a high (90%) chance of detecting a statistically significant difference at the 5% level between smokers and non-smokers when a difference of the size found in the present study actually exists. Only one published study, that of Underwood *et al.* (1969), satisfies this condition. For detecting the observed difference in neonatal mortality rates alone, a sample size of about 70,000 is required, and for only a 50% chance of detection the necessary sample size would be about 22,000.

These figures go some way towards explaining the conflicting evidence. The fact still remains, however, that in the studies of both Underwood *et al.* (1969) and Rantakallio (1969) and among Yerushalmy's (1971) white mothers the mortality ratios between smokers and non-smokers are small; being 1.06, 1.01, and 1.03 respectively. However, in these studies death rates are much lower than in the studies where larger mortality ratios are present—namely, the present study, that of Frazier *et al.* (1961), and among Yerushalmy's (1971) Negro mothers. Furthermore, where perinatal death rates are lower, the proportion of births of 2.5 kg or less also tends to be lower, being 7.2%, 4.2%, and 4.4% respectively in the former three studies and 6.7%, 13.9%, and 7.9% respectively in the latter three studies. If it is true that all or some of the mortality effect of smoking acts through reducing birth weight, thereby placing the child at greater risk, then it follows that the higher the mean birth weight of a population (and hence the lower the proportion of babies of 2.5 kg or under) the smaller will be the effect of smoking on perinatal mortality. This is so since the death rate begins to rise very steeply below 2.5 kg. Furthermore, the perinatal death rate of babies of 2.5 kg or less will vary with the availability and quality of obstetric services, which are likely to have differed considerably between the populations so far studied.

Although it is not possible with the information available from other studies fully to verify such population differences, evidence from the present study may shed some light. When the data are classified by the social class of the mother's husband, the percentage of babies of 2.5 kg or less in social classes I and II is 4.9; an incidence comparable to that reported by Rantakallio and among the white babies in Yerushalmy's study. The late fetal plus neonatal mortality ratio for smokers and non-smokers in social classes I and II is lower than the average, being 1.10 compared with 1.28. Although the difference between these two values does not reach statistical significance, a larger sample from social classes I and II may establish a statistically significant difference.

These suggestions point towards a possible explanation in terms of differing biological and obstetric characteristics in the various populations studied. It is difficult to invoke any other explanation for the differing mortality ratios which is also consistent with the birth weight reduction reported in all studies. It seems unlikely, for example, that the type or method

of smoking in the various populations could affect birth weight differently from mortality.

Finally, there remains the problem of "causation." Yerushalmy (1964, 1971) suggested that smoking is simply an index of a certain type of mother who also tends to have babies of lower than average birth weight. Some relevant facts emerge from the present data. The finding that a change in maternal smoking habits during pregnancy had the effect of putting the baby into a birth weight and perinatal mortality category associated with the new smoking habits points towards some kind of cause-effect relationship and is not compatible with Yerushalmy's hypothesis. This finding is further strengthened by the birth weight analysis which shows that the diminution in birth weight of the offspring of smoking mothers persists and is indeed little changed when allowance has been made for a number of other social and obstetric mediating factors.

These results would seem to have important implications for health education. If we assume that the difference in perinatal mortality between smokers and non-smokers in the U.K. has remained constant and that at least 30% of women currently smoke regularly after the fourth month of pregnancy, an estimate can be made of the potential saving in newborn lives per year if all these women could be persuaded to stop smoking during pregnancy. With the present (1970) overall live fetal and neonatal mortality rates, this might amount to a saving of approximately 1,500 babies each year in England, Scotland, and Wales. If a campaign were mounted along these lines it should also

be possible to monitor the effects of such a campaign on birth weight and mortality rates, and thus provide a test of the causal hypothesis.

We should like to express our thanks to the Executive Committee of the National Birthday Trust for permission to use these data, and to Dr. E. D. Alberman and Mr. M. J. R. Healy for their helpful comments. This work was partly supported by a grant from the Nuffield Foundation to the Department of Growth and Development, at the Institute of Child Health, and also by a grant from the Health Education Council.

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Possible Role of Malaria in the Aetiology of the Nephrotic Syndrome in Nairobi

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British Medical Journal, 1972, 2, 130-131

Summary

In a study in Nairobi, Kenya, 30 young adults with nephrotic syndrome were investigated in detail and a further 18 were studied less completely. In no case was evidence found to support a possible role for malaria in the aetiology of the syndrome.

Introduction

The nephrotic syndrome is generally held to be more common in the tropics than in temperate climates. A major reason for this has been thought to be the role of quartan malaria, especially in children (Gilles and Hendrickse, 1963). In Uganda quartan malaria has been implicated as an important aetiological factor in the nephrotic syndrome not only in children but also in adults (Kibukamusoke, Hutt, and Wilks, 1967).

No physician could work in Nairobi for long without being impressed by the number of adults presenting with the nephrotic syndrome. In investigating this syndrome it was thought sensible, in view of the findings in neighbouring Uganda, to consider among other things the possible role of quartan malaria.

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Methods and Subjects

A total of 48 consecutive adult patients with the nephrotic syndrome who were seen by us during a 12-month period at the Kenyatta National Hospital, Nairobi, were included in the study. The diagnosis of the nephrotic syndrome was established by means of the usual criteria (Barr *et al.*, 1972).

The possible role of malaria was investigated in three ways. (1) Detailed histories were taken with special reference to residence in a malarious area and to previous illness suggestive of malaria. (2) Thick and thin blood films taken on 10 separate days were searched for malaria parasites. (3) Malaria antibody titres were estimated by using an indirect fluorescent antibody technique with *Plasmodium falciparum* as antigen. This antigen cross-reacts to some extent with the other forms of human malaria. As a precaution 21 sera were also tested with a *Pl. malariae* antigen. On the same sample of blood serum IgG, IgM, and β_{1C} globulin levels were also measured by standard immunological techniques.

Results

Thirty patients with the nephrotic syndrome were examined fully by these methods. Less comprehensive studies were carried out on the remaining 18 patients. Of the 30 fully investigated patients 22 were female and 8 were male. Their ages ranged from 15 to 39 years, 24 of them being aged between 15 and 25 years.

Histories.—Twenty-two of the fully investigated patients were Kikuyu and lived in the central, higher, non-malarious area of Kenya, though six of these had at some time visited an endemic area. Five came from areas of Kenya where there is seasonal transmission of malaria and three came from areas of endemic