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Smoking in Pregnancy and Vitamin B₁₂ Metabolism

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British Medical Journal, 1972, **2**, 74-77

Summary

In pregnancy the level of serum vitamin B₁₂ is lower in women who smoke than in non-smokers. This finding occurs independently of social class, parity, or level of haemoglobin. In addition, the mean serum B₁₂ level tends to be less in women who are anaemic and is less in those women who have smaller babies. These findings may be an effect of the cyanide content of tobacco smoke, since cyanide may be detoxified by a mechanism which depletes the stores of vitamin B₁₂ in the body.

Introduction

Two factors of importance in obstetrics which seem to be directly related to tobacco smoking are the increased incidence of small babies (Lowe, 1959; Herriot, Billewicz, and Hytten, 1962; O'Lane, 1963) and the decreased incidence of toxæmia and hypertension (Duffus and MacGillivray, 1968). Various ways have been suggested by which these effects may be produced, but little attention has been paid to the cyanide content of tobacco. However, Wilson and Matthews (1966) showed an association between tobacco smoking, cyanide detoxication, and serum vitamin B₁₂ levels in both normal subjects and those with certain neurological disorders.

The present study was designed to investigate any relation between smoking in pregnancy and serum B₁₂.

Patients and Methods

All women attending an antenatal booking clinic at one Cardiff hospital had a serum B₁₂ estimation. Patients were included in the study regardless of the stage of pregnancy at which they first booked, but subsequently results were subdivided according to the period of gestation. Obstetric data and details of smoking habit were obtained from the Cardiff Births Survey records. Inquiry into the cigarette smoking habits of each patient was made retrospectively during the puerperium.

The method used in estimating the serum B₁₂ was that utilizing *Euglena gracilis* (Hutner, Bach, and Ross, 1956). In all, 847 women were examined at the time of their first clinic visit. After exclusion of those pregnancies ending in multiple births or stillbirths, the results for the remaining 826 were recorded (Fig. 1).

Included were 22 patients of non-Caucasian extraction. As religious habits are particularly likely to influence serum B₁₂ levels these patients were studied separately. Only 4 of the 22 had a serum B₁₂ below 100 pg/ml (two Hindus, one Moslem, and one Sikh), and the mean level of the group was 146.7 pg/ml, compared with 172.2 pg/ml for the Caucasian population. These patients were then included in the general analysis as they form an increasingly large part of the population of this country.

Fig. 1—Distribution of values of serum B₁₂

Results

Gestation Period.—Regardless of the period of gestation the mean level of serum B₁₂ among smokers is significantly less than among non-smokers (Table I). The difference is greatest in early pregnancy. Table II shows the fall in mean serum B₁₂ associated with increasing smoking. The 29 "ex-smokers" included in this table are those who stopped smoking in early pregnancy and are omitted from all other tables.

Parity.—No significant variation in serum B₁₂ was found among women of different parity, although the B₁₂ level tends to be lower among those who smoke regardless of their parity (Table III). The difference is least among women of high parity who, regardless of their smoking habit, may already have low B₁₂ stores.

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TABLE I—Serum B₁₂, Gestation, and Smoking Habit

	Period of Gestation			Any Gestation Period
	<20 weeks	20-30 weeks	>30 weeks	
Non-smokers:				
Number of cases	242	84	88	414
Mean serum B ₁₂ (pg/ml)	190.8	168.1	151.9	177.9
Standard deviation	70.9	73.8	58.9	70.8
% distribution	58.5	20.3	21.3	100
Smokers:				
Number of cases	184	89	110	383
Mean serum B ₁₂ (pg/ml)	170.1	161.7	148.3	161.9
Standard deviation	66.4	67.9	65.9	67.1
% distribution	48.0	23.2	28.7	100
All cases:				
Number of cases	426	173	198	797
Mean serum B ₁₂ (pg/ml)	181.9	164.8	149.9	170.2
Standard deviation	69.7	70.7	62.8	69.5

Analysis of variance for B₁₂ at period of gestation, $F = 15.3$. Significant at 1% level.

t Test between mean serum B₁₂ at 20 weeks' and at 30 weeks' gestation:

	t	P
Non-smokers	5.01	<0.001
Smokers	2.74	<0.01
All women	5.72	<0.001

t Test between mean serum B₁₂ of smokers and non-smokers tested at:

	t	P
20 weeks	3.09	<0.01
20-30 weeks	0.59	>0.05
30 weeks	0.4	>0.05
Any stage	3.28	<0.01

TABLE II—Serum B₁₂ and Amount Smoked

	No.	Mean Serum B ₁₂ (pg/ml)	Standard Deviation
Non-smokers	414	177.9	70.8
Ex-smokers	29	172.3	59.0
Smokers:			
1-4 cigarettes	58	164.2	59.5
5-9 "	103	172.6	73.7
10-19 "	152	156.3	64.7
20+ "	70	156.3	67.2

Analysis of variance, $F = 2.883$.
Significant between 1 and 5% levels.

TABLE III—Serum B₁₂, Parity, and Smoking Habit

	Parity			
	0	1	2	3+
Non-smokers:				
Number	178	115	54	67
Mean serum B ₁₂ (pg/ml)	187.7	172.5	177.7	161.3
Standard deviation	74.6	66.6	63.5	70.8
Smokers:				
Number	149	108	54	72
Mean serum B ₁₂ (pg/ml)	170.4	150.3	172.3	153.8
Standard deviation	69.6	54.7	84.2	61.8
All cases:				
Number	327	223	108	139
Mean serum B ₁₂ (pg/ml)	179.8	161.7	175.0	157.4
Standard deviation	72.8	62.0	74.3	66.2

t Test between mean serum B₁₂ of smokers and non-smokers:

Parity	t	P
0	2.17	<0.05
1	2.73	<0.01
2	0.38	>0.05
≥3	0.66	>0.05

Social Class.—There is a tendency towards a lower mean serum B₁₂ in women of lower social class but this finding does not reach levels of significance (Table IV). However, the difference between the mean serum B₁₂ of those women who smoke and those who do not is significant for all social classes except social class V.

Anaemia.—The mean serum B₁₂ level falls progressively with the level of haemoglobin in pregnancy, but for any haemoglobin level the mean B₁₂ level is less among women who smoke during pregnancy (Table V).

TABLE IV—Serum B₁₂, Social Class, and Smoking Habit

	Social Class			
	I and II	III	IV	V
Non-smokers:				
Number	123	93	118	62
Mean serum B ₁₂ (pg/ml)	184.3	190.3	179.7	162.9
Standard deviation	71.3	81.9	78.9	69.2
Smokers:				
Number	62	63	154	61
Mean serum B ₁₂ (pg/ml)	162.3	164.5	159.8	166.9
Standard deviation	68.6	61.9	79.7	65.0
All cases:				
Number	185	156	272	123
Mean serum B ₁₂ (pg/ml)	176.9	179.9	168.4	164.9
Standard deviation	71.0	75.3	79.8	66.9

Analysis of variance for social class, $F = 1.334$.
Not significant at 5% level.

t Test between mean serum B₁₂ of smokers and non-smokers:

Social class	t	P
I and II	2.03	<0.05
III	2.24	<0.05
IV	2.05	<0.05
V	0.33	>0.05

TABLE V—Serum B₁₂, Anaemia, and Smoking Habit

	Haemoglobin at First Clinic Visit		
	<60%	60-69%	≥70%
Non-smokers:			
Number	7	34	373
% distribution	1.7	8.2	90.1
Mean serum B ₁₂ (pg/ml)	140	149	181.2
Standard deviation	38.2	75.9	69.9
Smokers:			
Number	2	38	343
% distribution	0.5	9.9	89.6
Mean serum B ₁₂ (pg/ml)	130	131.5	165.4
Standard deviation	42.4	58.6	67.1
All cases:			
Number	9	72	716
Mean serum B ₁₂ (pg/ml)	137.8	139.8	173.6
Standard deviation	36.6	67.4	69.0

Analysis of variance for anaemia, $F = 9.18$.
Significant at 1% level.

t Test for mean serum B₁₂ of smokers and non-smokers:

Haemoglobin	t	P
<60%	0.3	>0.05
60-69%	1.08	>0.05
≥70%	3.08	<0.001

Serum B₁₂ and Hypertension in Pregnancy.—In this study "hypertension" is defined as a diastolic blood pressure of 90 mm Hg or a systolic blood pressure of 150 mm Hg recorded on at least two occasions before pregnancy or before the twentieth week. Mild or moderate pre-eclampsia is recorded when after the twentieth week of pregnancy the diastolic blood pressure rises above 90 mm Hg on at least two occasions accompanied by clinical oedema and/or proteinuria of less than 1 g/litre. Severe pre-eclampsia is defined when the above findings are associated with proteinuria of more than 1 g/litre. This study again confirms the lower incidence of both hypertension and pre-eclampsia in those who smoke. The mean serum B₁₂ is higher among hypertensive non-smoking women than among normotensive non-smoking women although lower in smokers who are hypertensive than in those who are normotensive (Table VI). The mean serum B₁₂ levels in the two groups do not show any statistically significant difference.

Serum B₁₂ and Infant Weight.—The increased incidence of small babies born to women smoking in pregnancy is again confirmed in this study. In those patients who had their B₁₂ level estimated before the twentieth week of pregnancy there are pronounced differences in B₁₂ levels between smokers and non-smokers, the greatest difference between the groups being found in women having babies weighing 2,500 g or less (Table VII). The mean B₁₂ level for both groups of women rises with infant size although not to a significant level.

TABLE VI—Serum B₁₂, Hypertension, and Smoking Habit

	Hypertension		Pre-eclampsia	
	No	Yes	Mild and Moderate	Severe
Non-smokers:				
Number	328	32	49	4
% distribution	79.4	7.8	11.9	1.0
Mean serum B ₁₂ (pg/ml) ..	174.5	201	182.9	212.8
Standard deviation	70.1	81.1	65.9	51.0
Smokers:				
Number	344	16	22	—
% distribution	90.1	4.2	5.8	
Mean serum B ₁₂ (pg/ml) ..	162.9	158.9	151.4	
Standard deviation	67.6	57.6	58.0	
All cases:				
Number	672	48	71	4
Mean serum B ₁₂ (pg/ml) ..	168.6	187.0	173.1	212.8
Standard deviation	69.0	64.8	51.0	
(2 cases with renal disease excluded)				

t Test = 1.7845 P>0.05 Non-smokers—hypertension and no hypertension.
 „ = 0.2692 P>0.05 Smokers—hypertension and no hypertension.
 „ = 1.09 P>0.05 Non-smokers—pre-eclampsia and no pre-eclampsia.
 „ = 0.892 P>0.05 Smokers—pre-eclampsia and no pre-eclampsia.

TABLE VII—Serum B₁₂ before 20th Week, Infant Weight, and Smoking Habit

	≤2,500 g	−2,950 g	>2,950 g
Non-smokers:			
Number	7	36	199
Mean serum B ₁₂ (pg/ml) ..	182.7	183.4	192.4
Standard deviation	37	55.7	73.7
Smokers:			
Number	7	42	132
Mean serum B ₁₂ (pg/ml) ..	142.9	167.0	171.7
Standard deviation	45.5	68.1	65.7
All cases:			
Number	14	78	331
Mean serum B ₁₂ (pg/ml) ..	162.8	174.6	184.1
Standard deviation	44.9	62.8	71.3

Analysis of variance for infant weight, F = 1.08.
 Not significant at 5% level.

t Test for mean serum B₁₂ of smokers and non-smokers:

Infant weight	≤2,500 g	..	..	t	P
„	−2,950g	..	..	1.8	>0.05
„	>2,950g	..	..	1.17	>0.05
„	„	..	..	2.67	<0.05 >0.01

Serum B₁₂ and Maternal Weight.—The weight of the patient at 20 weeks' gestation was recorded or computed on the basis of 0.5 kg a week weight gain taken from the nearest recorded weight. The mean serum B₁₂ is always lower among smokers than non-smokers of similar weight, and there is also a fall of mean serum B₁₂ with increasing maternal weight which does not reach levels of significance (Table VIII).

TABLE VIII—Serum B₁₂, Maternal Weight, and Smoking Habit

	Maternal Weight (kg)		
	<55	55-74	≥75
Non-smokers:			
Number	54	293	55
Mean serum B ₁₂ (pg/ml) ..	188.5	177.6	172.1
Standard deviation	75.5	73.0	59.7
Smokers:			
Number	63	264	51
Mean serum B ₁₂ (pg/ml) ..	174.8	159.5	156.7
Standard deviation	70.5	65.4	65.6
All cases:			
Number	117	557	106
Mean serum B ₁₂ (pg/ml) ..	181.2	169.0	164.7
Standard deviation	72.9	70.0	62.8

Analysis of variance for maternal weight, F = 1.84.
 Not significant at 5% level.

t Test for mean serum B₁₂ of smokers and non-smokers:

Maternal weight	<55 kg	..	..	t	P
„	55-74 kg	..	..	3.09	>0.05
„	≥75 kg	..	..	1.26	<0.01 >0.001
„	„	..	..		>0.05

Discussion

SERUM B₁₂ LEVELS IN PREGNANCY

Various factors may affect the level of serum B₁₂. In pregnant women the levels are known to be lower than in non-pregnant women of similar age (Boger, Wright, Bech, and Bayne, 1956; Temperley, Meehan, and Gatenby, 1968). There is a progressive fall in serum B₁₂ levels throughout pregnancy which is thought to be due to the concentration across the placenta of the vitamin by the fetus (Edelstein and Metz, 1969). A second possible cause is that the serum of pregnant women may contain an inhibitor to the growth of test organisms used in the assay of B₁₂ (Lawrence and Klipstein, 1967). Further, the haemodilution of pregnancy may play a small part in the total fall in serum B₁₂ level. There may also be changes in the serum B₁₂-binding capacity (Lowenstein, Brinton, and Hsieh, 1966).

Neither maternal age nor parity has been shown to be related to serum B₁₂ levels in pregnancy (Ball and Giles, 1964; Temperley *et al.*, 1968). Ball and Giles found an association between anaemia (particularly megaloblastic anaemia) and reduction in serum B₁₂ although Whiteside, Ungar, and Cowling (1968) found no association between serum B₁₂ and haemoglobin levels.

Attempts have been made to relate variations in the level of serum B₁₂ to abnormal pregnancy states. An increase in either premature delivery or retardation of infant growth, associated with low maternal B₁₂ levels, has been described by several workers (Temperley *et al.*, 1968; Whiteside *et al.*, 1968). Temperley's other finding was of a relatively low serum B₁₂ level among women with accidental haemorrhage unassociated with pregnancy toxemia as compared with that for women having toxemic accidental haemorrhage. Sure (1951), in a study of rats, was also able to show an increased incidence of stillbirths and neonatal deaths among animals fed on a vitamin-B₁₂-deficient diet.

EFFECTS OF SMOKING IN PREGNANCY

Smoking during pregnancy has been shown to affect the incidence of abortion, perinatal death, premature labour, infant weight, and hypertension in pregnancy.

The small baby born to a woman smoking during pregnancy may be born early or born small, the second effect being greater. Social class, poor maternal nutrition, and lack of appetite may affect fetal nutrition, but smoking may also have some direct inhibitory effect on fetal nutrition. Fetal nutrition may also be affected by the raised levels of carboxyhaemoglobin in those women who smoke (Heron, 1962). Montell (1964) described the part played by the enzyme carbonic anhydrase, which is diminished in amount in the cord blood of infants born to those women smoking in pregnancy.

Placental circulation may be affected either by the effect of nicotine or by actual placental separation. Nicotine has a complex effect on the circulatory system which according to Volle and Koelle (1970) is mainly vasoconstrictor although Coffman and Javett (1963) produced evidence that nicotine dilates calf muscle capillaries.

Constituents of tobacco other than nicotine have been largely ignored in discussions on the mode of action of smoking on fetal size and maternal blood pressure, although some animal studies have recently suggested that nicotine is either not or only partially responsible for the effects of smoking in pregnancy. Volle and Koelle (1970) described tobacco as consisting of between 0.5 and 8% nicotine, with pyridine and nitrogenous bases, plus only a very low concentration of hydrocyanic acid.

Younoszai, Peloso, and Haworth (1969) exposed groups of pregnant rats to one of three types of cigarette, tobacco, lettuce leaf, and lettuce leaf with added nicotine. All the rats therefore inhaled similar amounts of carbon monoxide and fetuses of all rats were growth-retarded, but in the rats exposed to tobacco cigarettes fetal weight was reduced more than in other groups.

Kirschbaum, Dilts, and Brinkman (1970) performed experiments on pregnant ewes. The animals were injected with nicotine or the smoking of cigarettes was simulated and although changes were produced in the cardiovascular function of the ewe, these changes were not reflected in the fetus, and the authors concluded that the adverse effects of maternal smoking stemmed from some chronic effect of smoking, not measured in the study, as the fetus seemed to be protected from effects of both nicotine and carbon monoxide.

SMOKING AND SERUM B_{12}

Cyanide is detoxicated in the body by three possible routes and is also excreted unchanged by the lungs (Swinyard, 1970). The principal route for cyanide detoxication is by combination with thiosulphate and requires rhodanase, a liver enzyme. Thiocyanate thus becomes the principal detoxication product of cyanide. Cyanide may also be combined with cystine and other amino-acids, which might become important in women with poor nutrition where competition between fetal protein needs and detoxication of cyanide could occur. A further detoxication mechanism is possibly that cyanide becomes combined with hydroxycobalamin to form cyanocobalamin, which has been described as physiologically inactive (Smith, 1961; Lindstrand, Wilson, and Matthews, 1966).

Smith (1961) showed that sublethal doses of cyanide when administered to rats caused depletion of liver B_{12} . It has been shown that the plasma thiocyanate concentration is higher in smokers than in non-smokers (Støa, 1957; Monekosso and Wilson, 1966; Wilson and Matthews, 1966). The condition of tobacco amblyopia is caused by failure of the normal mechanisms of cyanide detoxication, which may be due to relative or absolute deficiency of B_{12} ; the condition is also known to be associated with poverty and malnutrition (Darby and Wilson, 1967).

In the absence of such abnormalities B_{12} metabolism has been shown to be altered in smokers. Linnell, Smith, Smith, Wilson, and Matthews (1968) found the mean thiocyanate urinary excretion in smokers to be double that of non-smokers and was also able to show a negative correlation with serum B_{12} concentration. One mechanism suggested for these changes is that in subjects with relatively low serum B_{12} concentrations there is a reduced ability to detoxicate cyanide by pathways involving this vitamin so that detoxication by the thiocyanate pathway is increased. Alternatively, as shown by Wilson and Matthews (1966), the coexistence of high thiocyanate and B_{12} urinary excretion with the low serum B_{12} levels found among smokers may reflect B_{12} depletion resulting from the conversion of tissue cobalamin to cyanocobalamin. Such effects, although slight in normal subjects, might become significant in patients with marginal reserves of B_{12} .

Most of the work by Wilson (1968) and Wilson, Linnell, and Matthews (1971) has been in connexion with tobacco amblyopia, Leber's hereditary optic atrophy, and tropical neuropathy but Wilson also suggested a connexion between hypertension in pregnancy, cigarette smoking, and B_{12} metabolism.

SMOKING IN PREGNANCY, SERUM B_{12} , AND CYANIDE DETOXICATION

In suggesting a connexion between smoking in pregnancy and the level of serum B_{12} we have postulated a disorder related to cyanide detoxication.

Infant weight may be decreased in those cases where the mother already has poor body reserves of protein or serum B_{12} . In the former case the detoxication of cyanide, using essential amino-acids, may compete with fetal demand, and in the latter the already low B_{12} reserves of the mother may lead to increasing

detoxication of cyanide by the thiocyanate pathway. It is also possible that the low serum B_{12} levels found among those women who smoke in pregnancy may only reflect B_{12} depletion resulting from conversion of tissue cobalamin to cyanocobalamin.

A further possibility is that the presence of higher levels of cyanide in the serum of women smoking in pregnancy adversely affects the test organism used in the method of estimating serum B_{12} . This last postulation seems unlikely as Matthews (1962) found no effect on the growth of the test organism when high concentrations of cyanide were added.

Concerning the mechanism of the relative hypotension found in pregnant women who smoke it is possible to postulate that the thiocyanate produced in detoxication of cyanide is responsible. Thiocyanate was at one time used as a hypotensive agent (Nickerson, 1970). Thus women with already low stores of B_{12} who also smoke are those in whom the detoxication of cyanide by the B_{12} pathway is minimal, with increased use of the thiocyanate pathway.

Further work is required to study thiocyanate and cyanide levels in pregnancy and radioimmune assay of serum B_{12} , and to relate the results to normal and abnormal conditions found in pregnancy. The present study does, however, seem to furnish further evidence that smoking during pregnancy is particularly contraindicated in the patient with existing poor nutrition such as exists in those women of higher parity, lower social class, or with coexistent anaemia.

We wish to thank Mr. R. C. Cummin, Dr. J. Lawson, and Mr. V. R. Tindall for permission to study their patients. Mr. F. Lewis, F.I.M.L.T., was responsible for the serum vitamin B_{12} estimations.

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