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DIET AS A PROPHYLACTIC AGENT AGAINST PUERPERAL SEPSIS

WITH SPECIAL REFERENCE TO VITAMIN A AS AN ANTI-INFECTIVE AGENT

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In a previous paper (1929) on the treatment of puerperal septicaemia with preparations containing vitamin A we stated that an investigation was also being made into the possible prophylactic effect of such preparations against puerperal sepsis. We argued that if vitamin A had even a slight therapeutic effect in such a virulent infection as septicaemia it should be of much greater value as a prophylactic agent. It seemed possible that in the administration of vitamin A prior to labour we might have a valuable auxiliary method which would supply a missing factor so apparent in some cases even where every precaution against sepsis has been taken.

Experimental work on young animals suggested that vitamin A and carotene might well be described as " anti-infective " in their action, because when absent from or deficient in the diet, multiple infective foci develop, resulting in death unless the deficiency is made good (Green and Mellanby, 1928, 1930). The preventive and curative actions of vitamin A and carotene in the autogenous sepsis of the animals were equally great. It was obviously desirable to see whether these substances played any similar part in controlling the resistance of the human body to sepsis. This seemed possible, for the septic lesions which develop autogenously in animals on a vitamin A deficient diet are also commonly found in human beings. These include septic nasal sinuses, a catarrhal condition of nose and throat and respiratory passages, middle-ear disease,

broncho-pneumonia, pyelitis, and a septic condition of the genito-urinary tract. There is also reason to believe that the diet of many individuals in this country is deficient in vitamin A, the main sources of which are found in the more expensive foods—for example, milk, butter, eggs, and certain vegetables, while it is almost completely absent from cereals and cereal products and many other extensively eaten foods.

A study of the prophylactic action of vitamin A against puerperal sepsis in women suggested itself as a promising method of testing the clinical significance of the animal experiments. The duty of the maternal organism during pregnancy is to supply all the substances necessary for the growth of the embryo. These substances she either gets directly from her food, synthesizes them from the ingested foodstuffs, or, when these sources are insufficient, she supplies them from her own body stores as long as they are available. Many substances cannot be synthesized by the body, and must therefore come directly from her food or from her depots replenished by food. Now the body has a great capacity for storing vitamin A, especially in the liver. This store has its origin in the vitamin A, and most probably also in the carotene, of the food eaten (Moore). If the diet is deficient in these factors, as is probably the case in many individuals, the liver stores of vitamin A may be small, even at the beginning of pregnancy. The demands of the growing foetus will make these reserves still smaller, for, in addition to the supplies necessary for actual growth and metabolism, the foetus demands a reserve of vitamin A for its own liver. (H. N. Green examined eight foetal livers and found that six of them contained vitamin A in varying quantities.) These facts indicate that many women at childbirth will be deprived of most of their reserves of vitamin A and, if the animal experiments have any meaning in terms of the human subject, they will have less resistance to the invasion of pathogenic organisms at the time of parturition.

Apart from this evidence, however, there are other direct indications that women during pregnancy are specially liable to develop gross signs of vitamin A deficiency. Thus Birnbacher noticed that hemeralopia arising from lack of fat-soluble vitamins in the after-war years in Vienna was much more frequent during pregnancy, particularly towards the end of term and in women bearing heavy children.

Two other observations suggested the need for this investigation:

1. The infective foci found in animals following vitamin

A deficiency are particularly prominent in relation to squamous, columnar, and ciliated epithelium, and this is of special importance in the present instance, since puerperal sepsis is primarily an invasion of the epithelium of the generative organs by pathogenic bacteria.

2. H. N. Green has found that if rats, when pregnant, are given diets complete except for vitamin A, a large proportion of them ultimately develop chronic sepsis of the generative tract, while, on a complete diet at this time, control rats after pregnancy are unaffected in this respect. Nor are virgin rats so liable to develop this form of sepsis, even on a vitamin A deficient diet.

The usually accepted explanation of the frequency with which puerperal sepsis develops is that women during labour are more exposed to external infection. This is undoubtedly true, and might be accepted as a full explanation if all straightforward parturitions without intervention, or even parturitions carried out by the most complete asepsis practicable, escaped this complication. Unfortunately modern obstetrical technique has not had the complete success which would be expected if this were the whole explanation.

It seemed to us that the margin of safety as regards sepsis in childbirth must often be very narrow, and it was with the object of attempting to increase this margin and, at the same time, of testing our hypothesis based on the foregoing evidence, that the following inquiry was made. (A brief account of this work at an earlier stage was given by one of us (E.M.) at the Public Health Congress, 1930.)

Method of Investigation

About 600 women were involved in the present investigation. All cases not delivered in hospital were rejected from the series, so that a total of 275 women treated with the vitamin preparation and 275 untreated to serve as controls remain for analysis.

Pregnant women attending the ante-natal clinic were instructed to take half a teaspoonful of the preparation daily, commencing one month previous to the calculated day of labour. A fortnight's supply was given at a time. Theoretically, therefore, 1½ oz. of the vitamin preparation radiostoleum, an amount equivalent in vitamins A and D roughly to 30 oz. of a good cod-liver oil, should have been taken during the month. The investigation began in November, 1928. The first seventy-six cases prior to June, 1929, were given the preparation for only fourteen days before delivery. It was, however, continued for the

first seven days of the puerperium. It was then decided that a more logical procedure would probably be to begin the administration earlier and thus build up a larger reserve at the time of labour. In these cases none was given after admission to hospital. The cases were in no way selected ; the first patient was given the preparation and the next due for delivery about the same time was indexed as a control. The vitamin and control groups were thus equally distributed in point of time ; seasonal and epidemic or contagious influences predisposing to infection therefore tend to be equal in the two groups. It was considered that this method would give more uniform conditions than treating random groups of ante-natal patients with the preparation and considering all the remaining untreated ante-natal cases as controls.

Of the cases, 440 attended the Jessop Hospital ante-natal clinic and were delivered at this hospital ; 110 attended the municipal ante-natal clinic and were delivered at the Nether Edge municipal hospital. The two series have been classified together, as the number of cases and the incidence of sepsis in the smaller group is too small to warrant analysis.

Radiostoleum, the vitamin preparation used in this investigation, contains sources of vitamins A and D dissolved in a neutral oil ; 1 c.cm. of the preparation contains 150 blue units (Carr and Price) of vitamin A and 5,000 units of vitamin D in the form of irradiated ergosterol. British Drug Houses, Ltd., have kindly supplied the whole amount used in this investigation.

Results

In Table I the results are classified on the basis of the B.M.A. standard for puerperal morbidity—that is, all cases with two rises of temperature of 100° F. or over, between the end of the first and the end of the eighth day after delivery. This standard was adopted since it is the one in use for statistical purposes at the hospitals concerned, and thus allowed of a direct comparison between the figures in the experimental series and those obtained in previous years at the same hospital.

It will be seen from this table that the number of primiparae in each group was almost equal, as was the number which had some form of manual or instrumental intervention. The number of complicating factors during labour tends also to be equally distributed in the two groups. In the vitamin group there were only three morbid cases on the B.M.A. standard, an incidence of 1.09 per cent. In the control group there were thirteen

TABLE I.—*Effect of giving Vitamins A and D before Puerperium on Incidence of Puerperal Sepsis*

	Vitamin Group	Control Group
Number of cases	**275**	**275**
Primiparae	**147**	**145**
Complications of pregnancy or labour:		
Perineal tear	37	26
Contracted outlet	15	15
Low forceps	19	18
Breech	7	3
Twins	3	1
Internal version	2	0
External version	1	0
Craniotomy	1	0
Manual removal placenta	1	0
Post-partum haemorrhage	1	0
Precipitate labour	1	0
Primary uterine inertia	4	3
Albuminuria of pregnancy	6	4
Mitral stenosis	2	2
Pulmonary tuberculosis	1	0
Caesarean section	0	5
Accidental haemorrhage	0	1
Placenta praevia	0	1
Ante-partum eclampsia	0	1
Manual or instrumental intervention	**26**	**27**
Cases morbid (B.M.A. standard)	**3 (1.1 %)**	**13 (4.7 %)**
Cystitis (*B. coli*)	1	Cystitis: *B. coli* 4
Following manual rotation for posterior position	2	Staphylococcus 1
		Bacilluria: Streptococcus 1
		Acute mastitis 2
		Septic endometritis 2
		Acute bronchitis 1
		Septicaemia 1
Puerperal pyrexia*	**53 (19.2 %)**	**85 (30.9 %)**
Cystitis (*B. coli*)	5	Cystitis: *B. coli* 4
Endometritis	4	Staphylococcus 1
Acute mastitis	2	Urinary infection 1
Gonorrhoea	1	Acute mastitis 3
Retained clot	1	Endometritis 6
Septic perineum	2	Cervicitis 1
		Influenza 1
		Thrombo-phlebitis 1
		Septic perineum 3
Maternal mortality	**0**	Septicaemia (*Streptococcus haemolyticus*) **1**
Infant morbidity	**13**	**9**
Deaths: Stillborn	8	Stillborn 6
Premature	1	Pneumonia 1
Pneumonia	1	Sepsis 1
First day, cause unknown	2	Second day, cause unknown 1
Third day, cause unknown	1	
Illness: Pemphigus	1	Pemphigus 2
Jaundice	1	Melaena 1

* Temperature of 99° F. or over on one or more occasions after first day until discharge—not including B.M.A. cases.

morbid cases, an incidence of 4.73 per cent. The difference, 3.64 per cent., is over twice the standard error (1.43) and is therefore statistically significant. It is worthy of note that in the five cases of Caesarean section, one of accidental haemorrhage, and one of placenta praevia included in the control group, no morbid case occurred.

In Table II it will be seen that the morbidity rate for the two groups combined was much lower than that of previous years for the whole of the ante-natal patients. The control group for the Jessop Hospital shows a morbidity rate of 5.8 per cent., compared with an average

TABLE II.—*Morbidity Rate in Ante-natal Cases delivered at the Jessop Hospital in the Three Years Prior to which Present Investigation was commenced as compared with that in Cases covered by Present Investigation.*

Year	No. of Deliveries		B.M.A. Morbid Cases	Maternal Mortality
			Per cent.	Per cent.
1926	Ante-natal	585	**5.0**	1.0
	Total cases	795	9.6	2.9
1927	Ante-natal ...	553	**8.1**	1.1
	Total cases	812	12.4	2.6
1928	Ante-natal	662	**7.3**	1.5
	Total cases ...	963	9.9	2.6
Cases included in investigation during period November, 1928–June, 1931				
Total cases Jessop Hospital ...		410	3.4	0.3
Vitamin group		204	**1.0**	0.0
Control group		206	**5.8**	0.5
Total cases Jessop and Municipal Hospitals		550	2.9	0.2
Vitamin group		275	**1.1**	0.0
Control group		275	**4.7**	0.4

morbidity of 6.8 per cent. for the three years previous to which this investigation was begun. The morbidity rate for ante-natal patients was much lower than that of hospital cases in general, and appears to be improving. The vitamin group delivered at the Jessop Hospital shows a morbidity rate of 1 per cent., which, compared with those of the control group (5.8 per cent.) and of the ante-natal cases over the previous three years (5 per cent., 8.1 per cent., and 7.3 per cent.), shows a significant difference.

In Table I all cases which have shown any degree of puerperal pyrexia other than those of the B.M.A. standard have also been tabulated. Obviously many of these cases were not septic, since a rise of temperature which is not maintained can arise from other causes, but this type of case should tend to be equally distributed in the two groups, as the figures in Table IV indicate. The total number of pyrexial cases in the vitamin group was 56, an incidence of 20.4 per cent., and in the control group 98, an incidence of 35.6 per cent. The difference

of 15.2 per cent. is almost four times the standard error (3.83), and is therefore significant. It may be noted here that an analysis of the results at various stages of the investigation has shown the same relative difference in the incidence of pyrexia at each analysis.

In the total 550 cases there was one maternal death.

The classification of morbidity on any arbitrary standard such as that of the B.M.A., though useful, gives an incomplete summation of the incidence of sepsis, particularly where, as in the B.M.A. classification, no note is taken of septic cases occurring after the eighth day. The notifiable standard under the Public Health Regulations overcomes this difficulty to some extent ; it includes cases in which, on the bi-daily chart, a temperature of 100.4° F. or over occurs twice in three successive readings during the twenty-one days following delivery. Using this standard, as seen in Table III, there were 11 morbid cases in the vitamin group, and 15 in the control group.

TABLE III.—*Morbid Cases in Two Groups classified on Notifiable Standard*

	No of Cases	No. Morbid	Percentage Morbid
Total	550	26	4.7
Vitamin group	275	11	4.0
Control group	275	15	5.5

If we had adopted this standard alone without further analysis, and assessed our conclusion on it, we should have concluded that the vitamin treatment had little or no effect on the incidence of sepsis in the puerperium. On the other hand, if we compared the incidence on this standard with that on the B.M.A. standard, it might appear that prophylaxis with vitamin A had delayed the onset of sepsis until a later stage in the puerperium.

It is possible that the vitamin reserve built up at the time of labour had been exhausted during labour and the first week of lactation, and so the resistance of the vitamin group at this stage fell nearer to that of the control group. This, however, is conjecture, and it seemed that a comparison of the clinical severity of the septic cases in the two groups would assist in arriving at some conclusion. We have shown that the difference in the number of pyrexial cases is significant. If, therefore, the number of cases ranged according to a rough standard of clinical severity tend to be distributed in similar proportion in the two groups, this would indicate that the

incidence of sepsis of a major type was significantly greater in the control group.

Table IV shows that this is so, for while there were 10 cases in the control group which had pyrexia lasting from one to three weeks, there were only 4 of this type

TABLE IV.—*Cases arranged according to severity as indicated by Duration of Pyrexia*

	Vitamin Group		Control Group	
Number of cases	**275**		**275**	
Pyrexial cases	**56**		**98**	
1. Severe sepsis*	**4**		**10**	
Cystitis (*B. coli*)	2		Cystitis: *B. coli*	3
Septic endometritis and *B. coli* cystitis	1		Staphylococcus	1
Septic endometritis	1		Septic endometritis	2
			Septicaemia	1
			Mastitis	1
			Thrombo-phlebitis	1
2. Less severe†	**8**		**16**	
Cystitis (*B. coli*)	2		Cystitis: *B. coli*	3
Mastitis	2		Staphylococcus	1
Engorged breast	1		Streptococcus	1
Endometritis	2		Mastitis	4
Retained clot	1		Endometritis	5
			Acute bronchitis	1
			Pulmonary embolism	1
3. Moderate‡	**18**		**30**	
B.M.A. morbid cases	2		B.M.A. morbid case	1
Septic perineum	2		Septic perineum	3
4. Mild§	**26**		**42**	
B. coli cystitis	1		*B. coli* cystitis	1
			Cervicitis (streptococcus)	1
			Urinary infection	1
			Sapraemia	1

* Temperature raised to 99° F. or above for one to three weeks.
† Temperature raised to 99° F. or above for two to six days with definite local infection.
‡ Temperature raised on more than one occasion to 99° F. or above after first day, but no local infection definitely diagnosed (excluding septic perineum).
§ Temperature raised only once after first day to 99° F. or above.

in the vitamin group, and the distribution according to clinical severity is practically identical throughout. All the cases under the first two headings had some definite local infection. There were 12 of this type in the vitamin group and 26 in the control group. It appears, therefore, that the smaller incidence of pyrexial cases in the vitamin group does indicate a smaller incidence of sepsis as compared with the control group.

Effect of Intervention

Table V shows that 26 cases in the vitamin group and 27 in the control group were subjected to some form of manual or instrumental intervention of a major kind. These accounted for 2 morbid cases (B.M.A.) of the 3 in the vitamin group, and 3 morbid of 13 in the control

TABLE V.—*Incidence of Sepsis in Cases submitted to Intervention*

	Vitamins A and D	Controls
Number of cases	26	27
Morbid cases (B.M.A.)	2	3
Pyrexial cases	7	15
Severe	0	3
Less severe	0	3
Moderate	4	5
Mild	3	4

group. None of the vitamin group with intervention developed any local infection, while 6 of the control group with intervention had local infection—3 classified as severe and 3 as less severe. There were in all 7 pyrexial cases in the vitamin group with intervention, and 15 in the control group with intervention.

Infantile Morbidity

There is nothing significant in the incidence of sepsis in the infants born in the two groups, nor was any difference observed in the progress of the infants during the short period they were in hospital.

DISCUSSION

We believe that these results indicate that the administration of vitamin A during the last month of pregnancy has diminished the liability to a morbid puerperium. It seems that the incidence of sepsis, particularly in the early period of the puerperium, in which the most dangerous types of sepsis are liable to arise, has been lowered by increasing the vitamin A intake. It was not, of course, to be expected that this would cause a complete disappearance of sepsis. Probably no measure which increases the systemic or local resistance will prevent the development of pyrexia if the bacterial invasion is sufficiently great. An increased resistance should result in a decreased number of cases of puerperal pyrexia, and a decrease in clinical severity and duration of infection in those cases infected. This tendency can be observed in the difference between the treated and non-treated cases in this series. It must be emphasized also that there was no certainty that all the women ordered to take the vitamin preparation actually took it. Some individuals found it unpleasant, and it is probable that at least a small proportion of cases did not take the preparation. This

possibility makes the positive interpretation of our results more likely.

The preparation given contained a fair amount of vitamin D as well as vitamin A. On experimental grounds we are inclined to believe that vitamin D has little anti-infective action ; it was thought, however, that it might prove of significance in connexion with other obstetric difficulties, such as uterine inertia, but on this point we have obtained no evidence. The possibility cannot be denied, however, that the results described may be due, in part at least, to the presence of increased vitamin D in the diet. To ensure a normal calcium metabolism it is essential that the diet of the pregnant woman should contain some source of vitamin D. Now vitamin D is often closely associated with vitamin A in nature, although not so widely distributed, so that whether the ordinary food contains sufficient vitamin D, or whether it is given as a supplement such as cod-liver oil, a good supply of vitamin A is likely to be assured.

Our experimental and clinical results indicate that an adequate supply of vitamin A must be given to the pregnant woman. It should be the aim of all concerned with ante-natal welfare to see that the diet is rich in natural sources of vitamin A. Milk, egg yolk, green vegetables, carrots, and butter should be taken unsparingly, as long as over-eating is avoided by reduction in the cereal and meat content of the diet to a level where a healthy appetite is developed. Mammalian liver is an excellent source of vitamin A, and should be included in the diet at least once weekly unless otherwise contraindicated. If a well-varied natural diet of this kind is taken, an adequate supply of the other important nutritional factors is assured. These include the other known accessory food factors—vitamins B (complex), C, and D—together with the inorganic elements—calcium, phosphorus, iron, copper, manganese, and iodine—all essential for the pregnant woman.

Where this complete diet cannot be taken for economic or other reasons, it should be supplemented by some preparation rich in vitamins A and D. Cod-liver oil is the cheapest source, but where a dislike to this oil exists a reliable commercial preparation rich in these vitamins is indicated. The best line of action is undoubtedly to regulate the diet during pregnancy and lactation along the lines indicated, and, if this is done, there may be no need for supplementary rich sources of the fat-soluble vitamins. Where social conditions are poor, however, or

where the course of labour makes the occurrence of infection probable, some preparations of this kind should be of value as a prophylactic measure. The same course of dietary should also be adopted throughout the puerperium and lactation so as further to increase the resistance.

Summary

1. This investigation relates to 550 pregnant women attending the out-patient department of the ante-natal clinics of Sheffield, and subsequently delivered in hospital.

2. Alternate women were given an extra supply of vitamins A and D during the later weeks of pregnancy (usually for one month, but in some cases for a fortnight before delivery). Thus, 275 women received the vitamin supplement and 275 women acted as controls.

3. Of the vitamin-treated cases 1.1 per cent. and of the control cases 4.7 per cent. developed the B.M.A. standard of morbidity.

4. The results classified on the basis of duration of pyrexia also suggest that the vitamin preparation increased the resistance of the puerperal women to infection.

We wish to express our thanks for the facilities for carrying out this investigation offered to us by the honorary staffs of the Jessop and Nether Edge Hospitals. We are also greatly indebted to Dr. M. Walker for assisting us with the cases investigated at the Sheffield Ante-Natal Clinic, and to Dr. Matthew Young for examining the results statistically. The expenses of this investigation have been provided by the Medical Research Council, to whom our thanks are due.

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