A possible preventive effect of low-dose fish oil on early delivery and pre-eclampsia: indications from a 50-year-old controlled trial

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A preventive effect of dietary marine *n*-3 fatty acids on early delivery and toxaemia has recently been hypothesized. In only one published controlled trial fish oil has been given to pregnant women, namely in that conducted during 1938–9 in London by the People's League of Health with a dietary supplement containing vitamins, minerals, and halibut liver oil. Although it was of high quality and its findings are hitherto unexplained, neglect and misinterpretation of the trial seem to occur commonly in reviews. Of the 5644 women who were enrolled the 622 withdrawals were independent of treatment. Alternate allocation to treatment was used, producing two groups that were well balanced as to age and parity. The supplement was given from about week 20. The control group did not receive any supplement. Reductions of 20·4% (95% confidence interval 9–30%, $P = 0{\cdot}00083$) and 31·5% (95% confidence interval 11–47%, $P = 0{\cdot}0047$) were seen in odds of delivering before 40 weeks of gestation and pre-eclampsia respectively. No significant effects were seen on perinatal mortality, average birth weight, deliveries after 40 weeks, hypertension in the absence of oedema and proteinuria, duration of labour, sepsis or breast-feeding occurrence. Later controlled trials with vitamins or minerals given in the same amounts as in this trial have largely failed to show convincing effects as seen here. A controlled trial assessing the isolated effects of fish oil in pregnancy is warranted.

Dietary fish oil supplements: Vitamins: Minerals: Pregnancy: Early delivery: Pre-eclampsia

Half a century ago, the People's League of Health conducted a controlled trial in London with more than 5000 pregnant women in order to assess the effects of a dietary supplement consisting of vitamins, minerals and halibut liver oil (People's League of Health, 1942*a*, *b*, 1946). The supplemented group had fewer women with early deliveries and toxaemia. These findings have now become of revived interest as it was recently suggested on theoretical grounds that long-chain *n*-fatty acids, abundant in fish oil, may prolong duration of pregnancy (Olsen *et al.* 1986) and prevent toxaemia (Dyerberg & Bang, 1985; Romero *et al.* 1988). To our knowledge the London trial is the only controlled trial where fish oil has been given to pregnant women, and later controlled studies with minerals and vitamins given as in the London trial have failed to show convincing effects on early delivery and toxaemia risk (Susser, 1981; Hemminki, 1982; Kramer, 1988; Green, 1989).

The trial is also unique due to the fact that it is still, after 50 years, the largest controlled trial of dietary supplementation in pregnancy. Nevertheless it has been overlooked or misinterpreted by several authors reviewing the evidence for possible effects of dietary intervention during pregnancy. This neglect is undeserved as the trial was of good quality and its findings are still of scientific interest since they remain unexplained.

In the present paper, we re-analyse and reinterpret the trial according to the current perception of how to undertake controlled trials. We also propose a new explanation of the findings, namely that the *n*-3 fatty acids in the fish oil might have caused the observed effects.

EXPERIMENTAL

Outline of the trial

Sources of information. The main sources are the interim report (People's League of Health, 1942*a*, *b*) and the final report (People's League of Health, 1946). The discussions that took place at meetings and that were reported in the proceedings of the Royal Society of Medicine (1942) and the Nutrition Society (1944), furnished a few, but important, clues. No further details about the actual trial performance were revealed by searches and inquiries made at the Medical Research Council's Archives, the Wellcome Institute for the History of Medicine, London School of Hygiene and Tropical Medicine, St Mary Abbots Hospital, the Royal College of Obstetricians and Gynaecologists, and the Fawcett Library: one other publication based on the same data-set was, however, traced (Martin, 1947) and some interesting information, including two pamphlets (Nethersole, 1922; People's League of Health, 1943), was found about the League. Only information essential to the interpretation of the trial is given here.

Population, treatment allocation, and withdrawals. All pregnant women that from March 1938 to the end of 1939 attended the antenatal clinics of the ten participating hospitals in London were eligible, except for those whose pregnancy at entry had advanced beyond the 24th week and who suffered from any disease or physical abnormality (not further defined).

Strictly (Royal Society of Medicine, 1942, p. 67) alternate enrolment was used, and the success by which this procedure equalized the two treatment groups as to potential confounding factors is indicated by the similarity in the numbers of the two groups when they are being stratified according to parity (χ^2 0·28, df 1, $P = 0{\cdot}60$), age (χ^2 1·81, df 5, $P = 0{\cdot}87$), and according to parity and age at the same time (χ^2 4·82, df 11, $P = 0{\cdot}94$) (Table 1).

Of the 5644 women who were enrolled 494 withdrew on account of war (mainly evacuations), thirty-nine as they had twin births, and eighty-nine because they miscarried at an early stage. No further information is available on the women who withdrew, making it impossible to analyse the trial according to 'intention to treat'. However, the numbers left in the two treatment groups were very well balanced (2510 *v.* 2512), suggesting that the withdrawals were independent of whether the women received treatment or not.

Daily dietary supplements. These were: saccharated iron carbonate 1·2 g (eighteen grains), equivalent to 0·26 g ferrous iron; calcium lactate 2 g (thirty grains), equivalent to 0·26 g calcium; minute quantities of iodine, manganese and copper; adsorbate of vitamin B_1 containing all factors of the B complex known at that time (B_1 content standardized at 200 I.U./g; equivalent to 0·6 g thiamin/g) 1 g (fifteen grains); vitamin C (ascorbic acid) 0·1 g; halibut liver oil (vitamin A 52000 I.U./g, vitamin D 2500 I.U./g) 0·36 g (six minims), equivalent to 5·6 mg retinol and 0·0225 mg cholecalciferol. The supplements were provided by Messrs Vitamins Ltd, Crookes Laboratories, and Roche Products Ltd.

The amount of eicosapentaenoic acid plus docosahexaenoic acid provided in the halibut liver oil is estimated to about 0·1 g/d (Haug *et al.* 1988; R. Ackmann, personal communication).

Length of treatment. Of the women 288, 411, 414 and 417 received the treatment for < 15, 16–19, 20–23, and 24+ weeks respectively. Thus, the average length of treatment was about 20 weeks.

Statistical analyses. Odds ratios are used to express the effects of treatment; when testing

Table 1. *Distribution by age and parity of the women in the trial (People's League of Health, 1946)*

	Primiparae				Multiparae				All			
	Treated		Controls		Treated		Controls		Treated		Controls	
Age group (years)	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
15–19	90	5·9	84	5·6	8	0·9	9	0·9	98	3·9	93	3·7
20–24	514	33·6	527	34·8	142	14·5	168	16·8	656	26·1	695	27·7
25–29	633	41·4	623	41·2	371	37·9	349	34·9	1004	40·0	972	38·7
30–34	226	14·8	220	14·5	282	28·8	286	28·6	508	20·2	506	20·1
35–39	63	4·1	54	3·6	139	14·2	151	15·1	202	8·0	205	8·2
40–44	4	0·3	5	0·3	38	3·9	36	3·6	42	1·7	41	1·6
All ages	1530	100	1513	100	980	100	999	100	2510	99·9	2512	100

for heterogeneity of odds ratios across parity and age strata (interaction), a multiplicative model is thus being assumed.

RESULTS

Conditions related to toxaemia (Table 2)

In primiparae a significant effect of treatment was seen on pre-eclampsia, with a reduction of 31·1% (95% confidence interval (CI) 5–50%, $P = 0{\cdot}021$) in the odds in the treated group relative to the controls. A reduction of 28·3% (95% CI 4–47%, $P = 0{\cdot}026$) was seen in the odds of getting albuminuria in primiparae. No significant effect was seen on the occurrence of hypertension in the absence of oedema and proteinuria (odds ratio 0·86, 95% CI 0·73–1·02, $P = 0{\cdot}084$).

Although none of the effects was significant in multiparae, in general the same trends were seen in this group as in primiparae. Testing for heterogeneity of the odds ratios across the two parity strata was non-significant in all three comparisons, justifying a pooling of the strata. When analysing the parity strata together, treatment reduced the odds of getting pre-eclampsia by 31·5% (95% CI 11–47%, $P = 0{\cdot}0047$) and albuminuria by 29·4% (95% CI 10–45%, $P = 0{\cdot}0049$); no significant effect was seen on hypertension after eliminating those with albuminuria and oedema (odds ratio 0·95, 95% CI 0·83–1·09).

In treated primiparae, the occurrence of 'hypertension or albuminuria, or both' (a prewar standard for toxaemia (People's League of Health, 1942*a*, *b*, 1946)) differed according to length of treatment: this condition occurred in 25·0% (seventy-two of 288), 20·7% (eighty-five of 411), 27·5% (114 of 414), and 34·5% (144 of 417) in primiparae receiving treatment for < 15, 16–19, 20–23, and 24+ weeks respectively (χ^2 20·9, $P = 0{\cdot}0001$). The People's League of Health (1946) compared these rates directly with the overall rate in primiparous controls, 31·7% (479 of 1512), and they concluded that the findings 'suggest the existence of a saturation level with the 16 to 20 weeks treatment at which the best results are obtained', and a similar conclusion can be reached if the parity groups are combined. However, length of treatment will depend primarily on the gestational age at which the treatment is being commenced. As the gestational age at enrolment is likely to be associated with factors influencing the risk of toxaemia, the comparisons that the authors make may well be confounded by such factors. A valid comparison would require a similar stratification of the controls according to gestational age at the time when they were allocated to the control group. In our opinion, the findings presented do not justify any conclusions as to how this effect relates to length of treatment. No significant differences were seen between age groups in the effect of treatment on 'hypertension or albuminuria, or both'.

Pregnancy duration (Table 3)

In primiparae, a 19·9% (95% CI 5–32%, $P = 0{\cdot}012$) reduction in the odds of delivering earlier than 40 weeks was seen in the treatment group, whereas in multiparae a reduction of 21·2% (95% CI 2–36%, $P = 0{\cdot}028$) was seen. In the combined groups, a reduction of 20·4% (95% CI 9–30%, $P = 0{\cdot}00083$) was seen.

No significant effects were seen on the odds of delivering after 40 weeks of gestation.

Birth weight

No significant effects were seen on average birth weight. In primigravidae receiving treatment, mean birth weight was 7·18 (SE 0·03) lb (3·26 (SE 0·014) kg), whereas in those receiving no treatment it was 7·17 (SE 0·03) lb (3·25 (SE 0·014) kg) ($P = 0{\cdot}8$); in multiparae

Table 2. *Effects of dietary supplementation on conditions related to toxaemia (People's League of Health, 1946)*

	Primiparae		Multiparae		All*	
	Treated	Controls	Treated	Controls	Treated	Controls
Total *n*	1530	1512	980	999	2510	2511
Pre-eclampsia†						
n	69	97	31	46	100	143
%	4·5	6·4	3·2	4·7	4·0	5·7
OR (95% CI)	0·689 (0·50; 0·95)		0·677 (0·43; 1·07)		0·687 (0·53; 0·89)	
Statistical significance	$P = 0·021$		$P = 0·097$		$P = 0·0047$	
Albuminuria						
n	83	112	35	52	118	164
%	5·4	7·4	3·6	5·2	4·7	6·5
OR (95% CI)	0·717 (0·54; 0·96)		0·675 (0·44; 1·04)		0·706 (0·55; 0·90)	
Statistical significance	$P = 0·026$		$P = 0·076$		$P = 0·0049$	
Hypertension only‡						
n	332	368	179	166	511	534
%	21·7	24·3	18·3	16·6	20·4	21·3
OR (95% CI)	0·862 (0·73; 1·02)		1·121 (0·89; 1·42)		0·946 (0·83; 1·09)	
Statistical significance	$P = 0·084$		$P = 0·33$		$P = 0·43$	

OR, odds ratio, defined as the odds of the event of interest among the treated women divided by the odds of the event among the controls; CI, confidence interval.

* The tests for heterogeneity of odds ratio between the two parity strata were in all three comparisons not significant ($P = 0·95$, 0·82 and 0·072 respectively).

† Pre-eclampsia defined as hypertension plus albuminuria plus oedema.

‡ Hypertension in the absence of albuminuria and oedema (hypertension is defined as a systolic blood pressure above 140 mmHg or a diastolic blood pressure above 90 mmHg).

the difference between the two groups was 0·07 (SE 0·05) lb (0·03 (SE 0·023) kg) ($P = 0·16$), favouring the treated women (the way these data were reported (People's League of Health, 1942*a*, *b*) does not permit further analyses of the effects on birth weight).

Fetal and infant mortality

There were no significant effects on the occurrences of stillbirths, early neonatal deaths (death before 8 d), or perinatal deaths: the odds ratios (treated *v.* not treated) were 0·823 (95% CI 0·58–1·17, $P = 0·28$), 1·424 (95% CI 0·84–2·40, $P = 0·19$) and 0·978 (95% CI 0·73–1·31, $P = 0·88$) respectively (tests for heterogeneity across parity strata were non-significant in all three comparisons ($P = 0·64$, 0·54 and 0·83 respectively)).

Other comparisons

No significant differences were seen in duration of labour. Compared with controls, treated primiparae tended to have longer labour, whereas treated multiparae tended to have shorter labour (the mean differences were: −1·2 (SE 0·7) h ($P = 0·22$) and 0·4 (SE 0·5) h ($P = 0·57$) respectively).

No significant effects were seen on the occurrence of sepsis (overall odds ratio 1·096 (95% CI 0·81–1·48, $P = 0·55$)), nor on the proportion of live-born children who were breast fed (overall odds ratio 0·884 (95% CI 0·75–1·04, $P = 0·14$)).

Table 3. *Effects of dietary supplementation on risk of delivering before and after 40 weeks of gestation (People's League of Health, 1946)**

	Primiparae		Multiparae		All†	
	Treated	Controls	Treated	Controls	Treated	Controls
Total *n*	1530	1512	980	999	2510	2511
Under 40 weeks						
n	308	362	197	241	505	603
%	20·1	23·9	20·1	24·2	20·1	24·0
OR (95% CI)	0·801 (0·68; 0·95)		0·788 (0·64; 0·98)		0·796 (0·70; 0·91)	
Statistical significance	$P = 0·012$		$P = 0·028$		$P = 0·00083$	
More than 40 weeks						
n	161	160	109	101	270	261
%	10·5	10·6	11·1	10·1	10·8	10·4
OR (95% CI)	0·994 (0·89; 1·11)		1·11 (0·83; 1·48)		1·038 (0·87; 1·24)	
Statistical significance	$P = 0·96$		$P = 0·48$		$P = 0·68$	
Gestational age not stated						
n	1	1	0	3	1	4

OR, odds ratio, defined as the odds of the event of interest among the treated women divided by the odds of the event among the controls; CI, confidence interval.

* Information on gestational age was probably based on whether it was stated in the hospital record that the baby was born prematurely or postmaturely (in those days defined as 1 week before or after 40 weeks (Royal Society of Medicine, 1942, p. 65)): if it were calculated directly on the basis of the menstrual history one would have expected a much higher proportion of women classified as 'not stated'. A registered occurrence of prolonged pregnancies is likely to have been underestimated, as in those days prolonged pregnancy was regarded as a minor clinical problem compared with for instance, women delivering too early.

† The tests for heterogeneity of odds ratio between the two parity strata were in both comparisons non-significant ($P = 0·91$ and 0·56, respectively).

DISCUSSION

Although at least fifteen reviews appeared during the period 1974–1989 that dealt with the role of nutrition in pregnancy, we found only five that cited the trial (using Science Citation Index, Social Science Citation Index, and other sources). This becomes even more remarkable when noting that in three of the five reviews, the authors have a very dismissive view of the trial that does not seem to hold. Thus, Hemminki & Starfield's (1978) questioning of how the women were allocated to treatment is not justified: this matter is sufficiently clear since it is explicitly stated in a report from one of the meetings (Royal Society of Medicine, 1942) that strictly alternate enrolment was used, and there seems to be no reason to suspect that this procedure was not followed (see next paragraph). MacGillivray (1981) applies the same yardstick to the London trial as to other contemporary studies that gave rise to 'claims that supplementing the diet... lowers the incidence of pre-eclampsia', but none of his criticisms apply to the London trial. Among the points he is making is the problem of unreliable recordings of pre-eclampsia; it is interesting that Bell (Royal Society of Medicine, 1942, pp. 65–67), a contemporary critic of the trial who gained general support in his criticism from Fisher (1943), also raises this issue in relation to the recording of premature deliveries. As one would expect the treatment and the control groups to suffer the same way, insufficient, imprecise or unstandardized recordings of the clinical variables would tend to cover any true effects of the treatment: they cannot, however, explain the effects that were actually observed on early delivery and toxaemia. Worthington-Roberts (1985, p. 8) writing about the trial stated that no effects were seen on birth weight and incidence of prematurity, the latter being misleading, if not

wrong, as the occurrence of deliveries earlier than 40 weeks was indeed reduced; in addition, he omits to mention the reductions seen in the occurrence of conditions related to toxaemia. Examples of publications where one would expect the trial to be mentioned are the review by Räihä (1968) where an account is given on dietary supplementation studies, that by Kristal & Rush (1984) on maternal nutrition and duration of gestation, and in the book with reviews on various topics of nutrition in pregnancy published by the Tenth Study Group of the Royal College of Obstetricians and Gynaecologists (1983). We found two reviews that gave well-balanced, albeit brief, accounts of the trial: a later review by Hemminki (1982) and that by Green (1989).

The London trial certainly deserves much more attention and appreciation. Not only are the findings of undiminished scientific interest as they remain unexplained (see later), it is still, after 50 years, the largest controlled trial undertaken with dietary intervention in pregnancy (Susser, 1981; Hemminki, 1982; Kramer, 1988; Green, 1989). The methodological standard of the trial is, in addition, almost as high as one would require nowadays of a trial highlighting the combined effects of the supplements given. Randomization is indeed a safer procedure than alternate assignment to obtain equal groups, since in alternate assignment it is possible to figure out in advance in which group a particular woman will end up (Pocock, 1983, p. 60). However, the fact that the two groups were very similar with respect to parity and age substantiates the alleged strictly (Royal Society of Medicine, 1942, p. 67) alternate allocation, and this, in turn, suggests that the two groups are comparable with respect to other potential confounding factors. Seemingly no attempts were made to assess compliance among those who received the supplements or to secure that the controls did not take supplements on their own; however, such a contamination bias would tend to cover any true associations rather than to create spurious ones. No information is available about the procedure for the dispensing of the supplements: thus, the possibility cannot be ruled out that the treated women were subject to a more intensive antenatal care than the controls as they might have been seen more frequently at the clinics in order to receive the supplements. The only way to fully avoid such a co-intervention bias would be to carry out a placebo-controlled double blind trial, but even today it would hardly be possible to obtain full blinding as the taste of fish oil cannot be concealed efficiently.

The definitions used for toxaemia-related conditions do not conform with definitions of today. The International Society for the Study of Hypertension in Pregnancy recommends that pre-eclampsia is defined as hypertension plus proteinuria developing after 20 weeks of gestation in a previously normotensive non-proteinuric woman (Davey & MacGillivray, 1988). In the trial the term pre-eclampsia also required oedema while the group with albuminuria was a mixture of women with hypertension plus albuminuria and women with albuminuria only. The groups may also have included women with what is now called chronic and unclassified hypertension. Furthermore, the defining criteria for hypertension were diastolic blood pressure above 90 mmHg or systolic blood pressure above 140 mmHg while the current definition is narrower as it is based on the diastolic blood pressure only, requiring one measurement of 110 mmHg or more, or measurements of 90 mmHg or more 4 h apart. Finally, the definition of albuminuria is not given and may not have matched exactly with the definition of proteinuria of today. However, even if the sensitivity and the specificity of the diagnoses 'pre-eclampsia' and 'albuminuria' applied in the study may be well below 100% relative to the current definition of pre-eclampsia, the bias resulting from this misclassification will tend to reduce the strength of any true associations, as expressed by odds ratios, between treatment and pre-eclampsia risk: the effects seen can thus not be explained by this bias. The lack of effect on the occurrence of 'hypertension only', where those with hypertension plus albuminuria have been excluded, is difficult to interpret since treatment seemed to have an effect on the occurrence of albuminuria; unfortunately, no data were given for hypertension irrespective of albuminuria.

The absence of effect on the risk of delivering after 40 weeks may be explained on the basis of a possible under-reporting of such deliveries (cf. the note in Table 3). It may also be, however, that treatment only has an impact on the lower end of the gestational age distribution, which would also help explain the absence of a significant effect on average birth weight (unfortunately, it was not possible to assess the effect on the occurrence of low birth weight). The findings are too weak to draw safe conclusions concerning the effects on mortality: thus, with the sample size given, the statistical power to detect a 30% reduction in perinatal, fetal and early neonatal mortality at a 5% significance level is only about 50, 35 and 15% respectively.

In our opinion the trial provides firm evidence for a preventive effect of the treatment given on the risk of pre-eclampsia as well as on the risk of delivering earlier than 40 weeks of gestation. Later controlled supplementation studies with vitamins or minerals forming part of the treatment in the London trial have largely failed to produce any effects; the few controlled trials showing significant differences between the treatment groups in pregnancy duration or pre-eclampsia risk have all suffered from serious methodological shortcomings (cf. Hemminki, 1982; Kristal & Rush, 1984; Kramer, 1988; Green, 1989). Ca supplementation in doses that were five to ten times higher than in the London trial has recently been shown to reduce the risk of pregnancy-induced hypertension and increase mean duration of pregnancy in an Andean population in Ecuador with a low intake of Ca (Lopez-Jaramillo *et al.* 1989, 1990); the effects seem, however, to be dose-dependent and doses in the same low range as in the London trial have failed to exhibit any statistically significant preventive effects on toxaemia (Kawasaki *et al.* 1985; Marya *et al.* 1987).

However, the amounts provided should be seen in relation to the background intake of the pregnant women in the trial. Before the actual trial the investigators undertook a dietary survey comprising 1000 pregnant women attending four of the ten participating hospitals: in fact the vitamins and minerals provided in the trial aimed at making up the so-identified deficiencies (People's League of Health, 1946). Dietary deficiencies were found in great proportions of the women. Unfortunately the results are reported imprecisely and only in terms relative to some standards which are not defined: 70% were in 'shortage' of Ca, 98% did not have 'satisfactory' intake of iron, 50% had lower intakes of vitamins A, B_1 and C than they 'required' or than 'was really desirable'. The emphasis that can be laid on this information as evidence for dietary deficiencies, is weakened further when the authors later in the paper state that 'the general impression was that the women were on the average better nourished than had been expected from previous surveys of comparable groups of the ordinary population. Many of the women were clearly following advice given at the antenatal centers, and fresh fruit and eggs frequently entered into their daily diet. The same was true of milk ... There were, however, instances in which the dietaries were grossly defective.' Further, it is not at all clear whether the sample was representative of the 5000 women in the trial.

Probably the best (C. Petty, personal communication) estimates of dietary intakes during the trial period can be derived from the survey undertaken in the late 1930s by the Rowett Research Institute (1955), comprising more than 1300 households distributed over sixteen different districts in Britain. In the two London districts, Fulham and Bethnal Green, the estimated daily supplies of vitamins A (retinol equivalents), B_1 and C and iron were 0·8 mg, 1·0 mg, 66 mg and 11 mg respectively. The values, which represent means of all family members, may be compared with the recommended dietary allowances (RDA) of today for pregnant women (Recommended Dietary Intakes Around the World (1983)): 0·75 mg, 1·0 mg, 60 mg and 13 mg/d respectively. These comparisons suggest that the pregnant women in the study were not deficient in these nutrients. The supplemental dose of vitamins A and D and iron (5·6 mg, 22 μg and 0·26 g/d respectively) were on the other hand five-,

two- and 18-fold the recommended intake and may thus possibly have exerted pharmacological effects. Average Ca intake per family member in the two London districts was 0·5 g/d, i.e. around 40% of the RDA for pregnant women (1·2 g). This low intake is comparable with the intake in pregnant women in Ecuador, 0·3 g, where effects similar to those seen in the present study were found at a dose of 2·0 g (Lopez-Jaramillo *et al.* 1989, 1990) but lower doses were not tested in that population. So, although no controlled study has shown preventive effects on pre-eclampsia and early delivery at doses as low as in the London study, 0·23 g, it cannot be excluded that this dose had an effect in the seemingly Ca-deficient London women. No data were obtainable on vitamin D, Mn, Cu, or I.

The validity of these conclusions can be doubted for several reasons. Among the uncertainties are: the Rowett study sample was not random but was weighted intentionally on the side of poverty with an over-representation of working-class families with children and an under-representation of middle- and upper-class families; particularly, Bethnal Green was a poor area of London and the households chosen there included many with unemployed men (Rowett Research Institute, 1955). The dietary estimates are means of all persons in the survey; being heavily influenced by the many children, they are thus not direct estimates of the intakes in pregnant women. Finally, the data were stratified into six groups according to food expenditure per person, and a great variation was seen among the groups in dietary intakes; we have calculated a simple mean of the strata as it is not possible to know how they should be weighted in order to make the estimates comparable with the women in the trial.

Compared with other controlled trials undertaken with pregnant women, however, the London trial is unique as it is, to our knowledge, the only one where fish oil formed part of the treatment. This is interesting as it has recently been suggested that marine *n*-3 fatty acids may prevent early delivery as well as toxaemia. Its hypothesized effect on pregnancy duration was inspired by the findings of comparatively high birth weight and gestational age in the fish- and whale-eating populations of the Faroe Islands (Olsen *et al.* 1986). Although many other possible explanations for these differences may be imagined (see for instance Ackman, 1989) the hypothesis is biologically plausible as *n*-3 fatty acids may down-regulate the arachidonic acid-derived prostaglandins that are mediators of labour and cervical ripening (Hansen & Olsen, 1988).

The hypothesized preventive effect of *n*-3 fatty acids on pre-eclampsia risk (Romero *et al.* 1988) is in part thought to be mediated via an inhibition of the production of pro-platelet-aggregatory and vasoconstrictory thromboxane A_2. This hypothesis is thus indirectly supported by the accumulating evidence for a preventive effect of aspirin on pre-eclampsia risk, since aspirin inhibits cyclooxygenase in producing thromboxane A_2 (Schiff *et al.* 1989; Benigni *et al.* 1989). *n*-3 fatty acids have however a wider spectrum of potential actions than aspirin: they may also increase production of anti-platelet-aggregatory and vasodilatatory prostacyclin I_3, increase blood viscosity, lower blood pressure, reduce vasospastic response to catecholamines and angiotensin$_2$ and increase endogenous fibrinolytic activity, all of which could be of value in the prevention of pre-eclampsia (Secher & Olsen, 1990).

The daily amount of eicosapentaenoic acid plus docosahexaenoic acid given in the London trial, 0·1 g, was very low compared with most other supplementation studies with *n*-3 fatty acids (Gibson, 1988). Although being controversial, doses in this range have indeed been found to exert certain biochemical effects: in diabetes mellitus patients (Driss *et al.* 1984) and elderly patients (Driss *et al.* 1988), 0·05 and 0·15 g eicosapentaenoic acid/d given for 4 and 6 weeks respectively, was found to reduce platelet aggregation as well as thromboxane B_2 formation. Treatment was given for a much longer period in the London trial, 20 weeks, which is long compared with most controlled supplementation studies

published so far with long-chain *n*-3 fatty acids. The size of the dose must also be seen in relation to the background intake of marine *n*-3 fatty acids in the women participating in the study. According to the Rowett household survey (Rowett Research Institute, 1955) the fish intake in England in the late 1930s was 28 g/d (mean of the six expenditure groups). Although fat fish may have played a greater role at that time, particularly among poorer people (C. Petty, personal communication), total fish intake of Londoners today may not be very different from this figure. The intake of *n*-3 fatty acids in pregnant women in London today has been estimated to be around 0·2 g (Crawford *et al.* 1986): in these women the supplement would consequently increase the daily consumption by 50%. Finally, it needs to be taken into account that being pregnant may result in an altered metabolism of, and an increased demand for, long-chain *n*-3 fatty acids due to the growing fetus (Neuringer *et al.* 1988), making it very difficult to estimate the potential effects on eicosanoid metabolism of the dose given in the London trial on the basis of dose–effect relationships observed in fish oil supplementation studies with non-pregnant subjects.

It is of course impossible to tell with any certainty which of the components of the treatment given in the trial caused the effects observed. But, taken together with the results from later supplementation studies, the findings from the London trial do stress the need for a controlled trial assessing the isolated effects of fish oil supplementation in pregnancy.

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