European Journal of Clinical Nutrition (2007) 61, 976–985

0954-3007/07 $30.00
www.nature.com/ejcn

ORIGINAL ARTICLE

Duration of pregnancy in relation to fish oil supplementation and habitual fish intake: a randomised clinical trial with fish oil

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Objective: To examine the effect of fish oil supplementation on duration of pregnancy, conditional on the woman's habitual fish intake.
Design: Multicentre 1:1 randomised clinical trial of effect of fish oil in a high-risk population of pregnant women in whom habitual fish intake was assessed at randomisation.
Setting: Nineteen university delivery wards in seven European countries.
Subjects: Pregnant women with preterm delivery, intrauterine growth retardation (IUGR), or pregnancy-induced hypertension (PIH) in a previous pregnancy (group 1, $n=495$); with twin pregnancies (group 2, $n=367$); or with suspicion of IUGR or threatening preeclampsia in the current pregnancy (group 3, $n=106$). Women were stratified into low, middle, or high fish consumers.
Methods: The intervention group received fish oil capsules providing 2.7 g long-chain *n*-3 fatty acids per day (*n*-3 poly unsaturated fatty acids (PUFA)) from around week 20 (groups 1 and 2) or 6.3 g *n*-3 PUFA from week 33 (group 3). The control regimen was capsules with olive oil. Effect on timing of spontaneous delivery was examined by Cox regression, assuming elective delivery (occurring in 40%) as a censoring event. Analyses of effect of fish oil were intention to treat, and all analyses were adjusted for maternal smoking, age, and parity.
Results: In group 1, fish oil reduced the hazard rate of spontaneous delivery (HR) by 44% (95% confidence interval 14–64%) and 39% (16–56%) in low and middle fish consumers, respectively, with no detectable effect (−56 to 33%) in high fish consumers. In groups 2 and 3, no significant effect of fish oil was detected in any of the sub-strata defined by baseline fish consumption.
Conclusions: In pregnant women with previous pregnancy complications, fish oil supplementation delayed onset of delivery in low and middle, but not in high, fish consumers.
Sponsorship: March of Dimes Birth Defects Foundation, Concerted Action (ERB-BMH1-CT92-1906) and PECO (ERB-CIPD-CT94-0235) programmes of the European Commission, and the Danish National Research Foundation. Lube Ltd donated the oil capsules.
European Journal of Clinical Nutrition (2007) **61,** 976–985; doi:10.1038/sj.ejcn.1602609; published online 7 February 2007

Keywords: fish oil; fish intake; pregnancy duration; RCT

Introduction

It has been hypothesised that an increased intake of long-chain *n*-3 fatty acids, abundant in fat from fish, can delay timing of spontaneous delivery, possibly by influencing the prostaglandins involved in the initiation of delivery (Olsen

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Received 26 January 2006; revised 8 November 2006; accepted 10 November 2006; published online 7 February 2007

et al., 1986) or through an 'anti-arrhythmic' effect on the myometrial activity (Baguma-Nibasheka *et al*., 1999; Olsen *et al*., 2003). The hypothesis has been supported by some (Olsen *et al*., 1992; Olsen *et al*., 2000; Smuts *et al*., 2003) but not all (Bulstra-Ramakers *et al*., 1995; Onwude *et al*., 1995; Helland *et al*., 2001; Knudsen *et al*., 2006) randomised controlled trials (Olsen 2004; Makrides *et al*., 2006; Szajewska *et al*., 2006), and by some (Olsen *et al*., 1991; Olsen and Secher 2002) but, again, far from all (Olsen 1994; Olsen *et al*., 1995; Bjerregaard and Hansen 1996; Oken *et al*., 2004; Rogers *et al*., 2004; Thorsdottir *et al*., 2004) observational studies. Two recent meta-analyses of controlled trials concluded that fish oil probably prolongs pregnancy, but that the size of this effect, estimated from the pooled analyses, is most probably too small to be of any clinical significance (Makrides *et al*., 2006; Szajewska *et al*., 2006).

One possible reason for the discrepancy between the trials could be that baseline intake of *n*-3 fatty acids may have varied across the study populations. Results from a Danish trial support this contention as the estimated effect of fish oil tended to be greatest in women who, at randomisation, reported a low habitual fish intake (mean difference in pregnancy duration 7.4 days), whereas no effect was detectable in those reporting a high intake (–1.6 days); in the group with intermediate fish intake, the mean difference was 4.8 days (Olsen *et al*., 1992). The public health implications are potentially important, meaning that any recommendation to increase intake of *n*-3 fatty acids for the prevention of preterm birth should probably be given conditionally on the target group's fish consumption pattern. None of the other published trials addressed this issue however, probably because baseline data on diet were unavailable. We, therefore, made a reanalysis of data from a large multicentre European trial where such data were available for a large proportion of the women, but had not been used in the primary report as they were not part of the prior hypotheses (Olsen *et al*., 2000).

The present reanalysis addressed three different issues: (1) to what extent the finding of the Danish trial (Olsen *et al*., 1992) of differential effects of fish oil supplementation on timing of spontaneous delivery across groups, defined by habitual fish intake, could be replicated; (2) to what extent the habitual fish intake *per se* was a predictor of timing of delivery, assessed separately in women not receiving fish oil and in women receiving fish oil; and (3) to what extent the reported habitual intake of olive oil was a predictor of timing of delivery, an issue raised by some earlier studies (Olsen *et al*., 1992; Helland *et al*., 2001; Olsen 2004).

Subjects and methods

Subjects and design of study

The overall design was that of a multicentre, randomised, clinical intervention study (Olsen *et al*., 2000). It was hospital based with centres in Denmark, Scotland, Sweden, England, Russia, Italy, Belgium, Holland, and Norway, and approved by each local ethical committee. The overall aim was to test, in various types of high-risk pregnancies, the possible preventive effect of fish oil supplementation on risks of preterm delivery, intrauterine growth retardation (IUGR) and pregnancy-induced hypertension (PIH). The study consisted of two sections of trials: the prophylactic trials enrolled women after 16 weeks of gestation with an uncomplicated pregnancy who, in an earlier pregnancy, had experienced preterm delivery (before 259 days) (trial A), IUGR (below 5th percentile (Eriksen *et al*., 1985; Secher *et al*., 1986)) (trial B), or PIH (diastolic blood pressure >100 mm Hg) (trial C), and women with current twin pregnancies (trial D). The therapeutic trials enrolled women with threatening preeclampsia ($+/-$ IUGR) (trial E) or suspected IUGR (<10th percentile by ultrasonography (Eriksen *et al*., 1985; Secher *et al*., 1986)) (trial F) in the current pregnancy. The exclusion criteria were: diabetes mellitus in or before pregnancy; diagnosed severe fetal malformation or hydrops in current pregnancy; suspicion in current, or occurrence in an earlier pregnancy, of placental abruption; drug or alcohol abuse; regular intake of fish oil or of non-steroidal anti-inflammatory agents or other drugs with an effect on thrombocyte function or eicosanoid metabolism; allergy to fish products. In the therapeutic trials (E and F), an additional exclusion criterion was high probability of delivering soon after randomisation (estimated within 1 week).

For the purpose of the present paper, trials A–C were aggregated and denoted the *previous problems* trial, trial D was denoted the *twins* trial, and trials E and F were aggregated and denoted the *current problems* trial.

Intervention products and blinding

The treatment was fish oil (Pikasol: 32% eicosapentaenoic acid (EPA) 23% docosahexaenoic acid (DHA), and 2 mg tocopherol/ml), whereas the controls received olive oil (oleic acid [18:1*n*-9] 72%, linoleic acid [18:2:*n*-6] 12%). In the prophylactic trials (*previous problems* trial and *twins* trial), four capsules of either oil were given per day, providing 2.7 g *n*-3 fatty acids per day in the intervention group, whereas in the therapeutic trials (*current problems* trial) nine capsules were given per day, providing 6.3 g *n*-3 fatty acids per day in the intervention group. Both oils were provided in 1 g identically looking gelatine capsules.

Randomisation and allocation concealment

Restricted blockwise computer-generated randomisation (1:1, individual-based) was employed within strata defined by cross tabulating clinical centres against the six original (Olsen *et al*., 2000) clinical groups (trials A–F). Within each stratum, the size of the first block was always four, after which block sizes of four, six, and eight occurred in random order.

Data collection and definition of outcome
A trial entry form with extensive baseline information was filled in before randomisation; a follow-up form on course of pregnancy and the perinatal period was filled in within 4 weeks of delivery; these forms were mailed to the Coordinating Centre. Gestational age was assessed from early (prerandomisation) ultrasound if available, or else from data on last menstrual period using Naegeles rule. Induced vaginal delivery and pre-labour caesarean section were regarded as elective deliveries.

Baseline intake of fish and of olive oil
As results from the Aarhus trial had suggested (Olsen *et al*., 1992) that habitual intake of fish modified the putative effect of fish oil supplementation on length of gestation, food frequency questions were introduced into the trial entry form. However, recruitment had already been running for some time for the multicentre trial when that information became available to us. Therefore, not all women participating in the multicentre trial were asked these questions at randomisation, and analyses based on these questions were not presented in the main report (Olsen *et al*., 2000). The questions used earlier in the Aarhus trial (Olsen *et al*., 1992) were used again in the Danish centres and adapted for application in the Swedish, Norwegian, Scottish, and Dutch centres. For the purpose of the analyses presented here, an attempt was made to recode each set of questions such that cutoff points for high vs middle and middle vs low fish consumers were as similar as possible to those defined in the analysis of the Aarhus trial (Olsen *et al*., 1992).

In order to put equal emphasis on olive oil as on fish and fish oil from the point of view of the women, we also included standardised questions about women's habitual use of olive oil for cooking in the baseline interview. The idea was to keep those women allocated to the control group, who were able to identify the type of oil they had received, away from self-supplementing with fish oil, thus avoiding contamination bias. Later on, it has been raised as an issue that olive oil may not be inert but have effect on the duration of pregnancy *per se* (Olsen *et al*., 1992; Helland *et al*., 2001; Olsen 2004). To address this issue, we classified the women on the basis of these questions into low, middle, and high consumers of olive oil.

Statistical methods
Effects on timing of spontaneous delivery were assessed by Cox regression (proportional hazards model), regarding elective deliveries as censorings. All analyses were adjusted for maternal smoking (nonsmokers, 1–9 cigarettes per day, 10+ cigarettes per day), age (<20, 21–24, 25–29, 30–34, 35+ years), and parity. Interaction terms were included to assess interaction between fish oil supplementation and baseline fish intake. The validity of the Cox regression model relies on the assumption of independent censoring: that is, women having elective deliveries must not differ from the remaining women by being prone to giving birth particularly early or late, had they not had an elective delivery, unless, however, the characteristics of a woman explaining her tendency towards early/late delivery are included in the model as covariates. The covariate describing whether the woman received fish oil supplementation is included in the model, and hence censoring owing to knowledge of fish oil supplementation would not violate the model assumptions. All analyses were intention to treat, conditional on the presence of information collected at baseline regarding habitual fish consumption.

Results

The total data set vs the sub-sample for whom we had information on baseline fish intake
Roughly the same effects were detected in the sub-sample as in the overall data set, on which our earlier publication (Olsen *et al*., 2000) was based (Table 1). Thus, fish oil supplementation was associated with a significant reduction of the hazard rate in the *previous problems* trial, whereas no effect was seen in the *twins* trial, and a significant hazard rate reduction was seen in the *current problems* trial. The Kaplan–Meier survival curves in Figure 1 show the effects of fish oil supplementation in the three trials.

Effect of fish oil supplementation in strata defined by baseline fish intake
In the *previous problems* trial, fish oil reduced the hazard rate in women with low and middle baseline fish intake (hazard ratios 0.56 and 0.61, respectively), whereas no effect of fish oil supplementation could be detected in women with high baseline fish intake (hazard ratio 1.02) (Table 2). The Kaplan–Meier survival curves in Figure 2 show the differential effects of fish oil supplementation in the strata defined by baseline fish intake. In the *twins* trial, there was no effect of fish oil supplementation in either of the groups defined by baseline fish intake, although the ratio tended to increase across the three fish consumption strata (hazard ratios 0.79, 0.95, and 1.46, respectively) (Table 2). In the *current problems* trial, no trend was detected towards larger hazard rate reduction when baseline fish intake was low; in fact, although the point estimates were substantially reduced in all strata (hazard ratios 0.45, 0.72, and 0.39, respectively), none of the hazard ratios differed significantly from 1; this may reflect the small number of observations in each stratum of this trial.

Effect of baseline fish intake in each randomisation group (oil group)
In the *previous problems* trial, among women randomised to receive olive oil, there was a significantly increased hazard

Table 1 European multicentre fish oil trial in pregnancy

Trial	*Intervention group*	*Number of observations (N)*	*Proportion of elective deliveries*[a] *(%)*	*Gestational age, hazard rate ratio (95% CI)*	
				Crude[b]	*Adjusted*[c]
Previous problems	Fish oil	435	27.3	0.81 (0.69, 0.95)	0.79 (0.67, 0.93)
	Olive oil	463	27.6	1 (ref.)	1 (ref.)
Previous problems, sub-sample	Fish oil	237	29.8	0.68 (0.55, 0.84)	0.69 (0.55, 0.86)
	Olive oil	258	24.1	1 (ref.)	1 (ref.)
Twins	Fish oil	289	54.5	0.98 (0.77, 1.26)	0.99 (0.77, 1.28)
	Olive oil	290	54.2	1 (ref.)	1 (ref.)
Twins, sub-sample	Fish oil	183	56.4	1.03 (0.75, 1.41)	1.02 (0.74, 1.41)
	Olive oil	184	57.0	1 (ref.)	1 (ref.)
Current problems	Fish oil	80	59.2	0.47 (0.27, 0.80)	0.49 (0.29, 0.86)
	Olive oil	62	51.7	1 (ref.)	1 (ref.)
Current problems, sub-sample	Fish oil	59	60.3	0.56 (0.32, 0.99)	0.55 (0.31, 0.99)
	Olive oil	47	43.5	1 (ref.)	1 (ref.)

Abbreviation: CI, confidence interval.
Effects in overall sample ($n=1619$) vs effects in sample with information on diet at baseline ($n=968$). Shown are proportions of elective deliveries and gestational age hazard rate ratios (fish oil vs olive oil).
[a]Based on subset with information on whether the delivery was spontaneous or elective ($n=1563$ in overall sample, $n=939$ in sub-sample with information on diet at baseline).
[b]Based on subset with information on gestational age and whether the delivery was spontaneous or elective ($n=1557$ in overall sample, $n=935$ in sub-sample with information on diet at baseline).
[c]Adjusted for maternal smoking (nonsmokers, 1–9 cigarettes per day, 10+ cigarettes per day), age (<20,21–24,25–29,30–34,35+), and parity. Based on subset with information on gestational age, confounders, and whether the delivery was spontaneous or elective ($n=1481$ in overall sample, $n=927$ in sub-sample with information on diet at baseline).

rate in low and middle fish consumers (hazard rate ratios 1.72 and 1.55, respectively) compared to high fish consumers. In women randomised to receive fish oil, however, no hazard rate increase was found in the low or middle fish consumers compared to high fish consumers (hazard ratios 0.94 and 0.92, respectively) (Table 3). Figure 3 shows the corresponding Kaplan–Meier survival curves.

In the *twins* trial and the *current problems* trial, patterns seemed less clear (Table 3). There was no significant effect of baseline fish intake in either of the randomisation groups. In the *twins* trial control group, however, the hazard rate tended to be increased, albeit insignificantly, in low vs high fish consumers (hazard ratio 1.48).

Test for interaction between effects of fish oil supplementation and of baseline fish intake

None of the tests for interaction between effects of fish oil supplementation and habitual fish intake exhibited significant results at the conventional *P*-level (Table 2). Thus, the apparent differential effects of fish oil supplementation, depending on baseline fish intake, was not significant when testing equality of hazard rate ratios across baseline fish intake groups, and equivalently, the apparent differential effects of baseline fish intake depending on randomisation group (oil group) was not significant. Among the three interaction tests, that for the *previous problems* trial had the lowest *P*-value (0.10).

Elective deliveries

The results reported above relied heavily on the information on elective deliveries, which occurred in 40% of the women in the trial. Thus, no significant effects of either fish oil supplementation or baseline fish intake on timing of delivery could be detected when this information was ignored (data not shown). The proportion of elective deliveries tended to occur differentially across the various groups (Table 2). Notably, the proportion was high in fish oil supplemented women when baseline fish intake was low and high in olive oil supplemented women when baseline fish intake was high; in the olive oil supplemented women, the proportion tended to increase with baseline fish intake.

Effect of baseline olive oil intake on timing of spontaneous delivery

Table 4 is similar to Table 3 except for the fact that baseline habitual use of olive oil for cooking is considered rather than baseline fish intake. There was no evidence of an effect on timing of spontaneous delivery of baseline olive oil intake in either of the randomisation groups.

Discussion

We found that the delaying effect of fish oil supplementation on timing of spontaneous delivery tended to occur differentially according to baseline intake of fish. In the largest

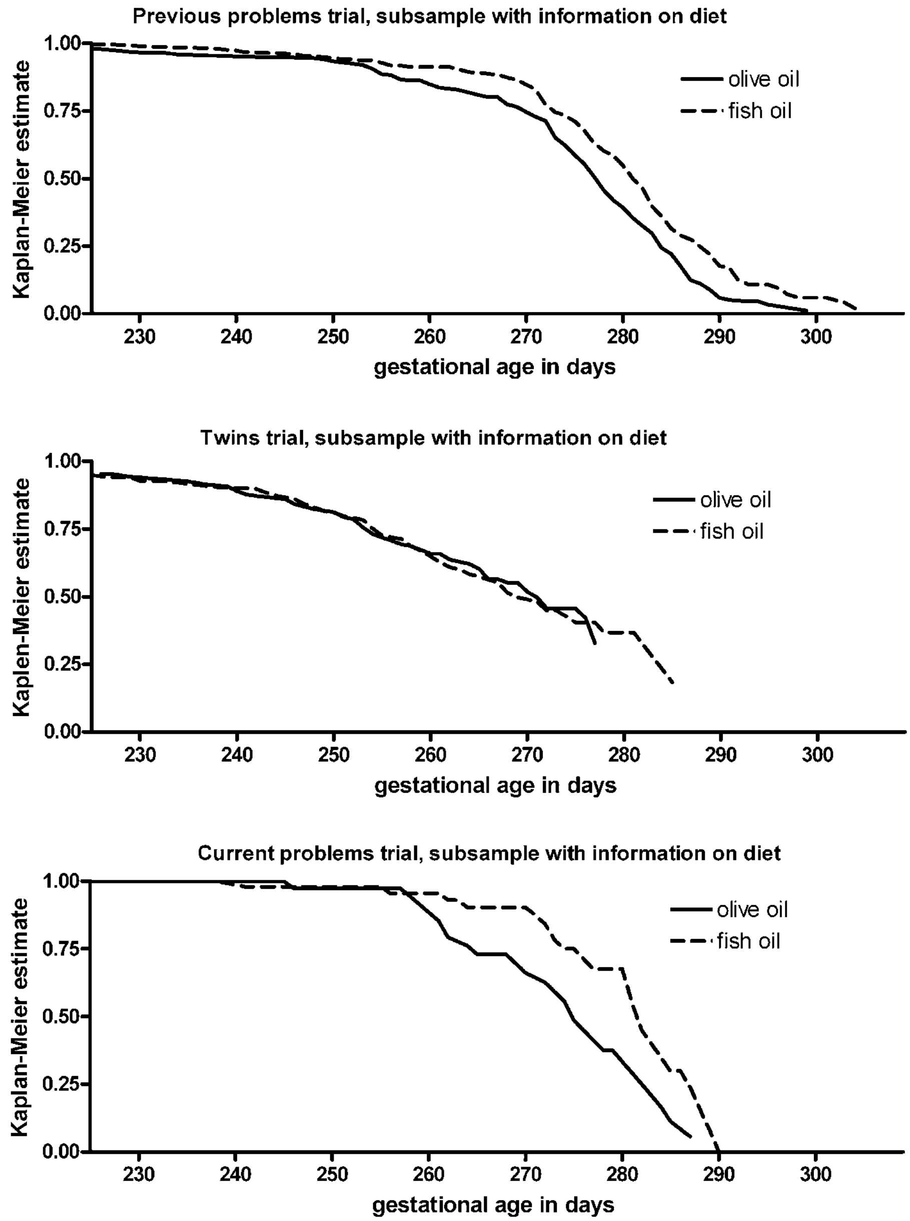

Figure 1 Kaplan–Meier survival curves. Survival time is the time of spontaneous delivery, and elective deliveries are considered censoring events. Stratified by intervention group (fish oil/olive oil) and trial.

section of the trial (495 women with singleton pregnancy and complications in a previous pregnancy), we only saw the effect of fish oil supplementation in women with low and middle fish intake, whereas no effect was observed in women reporting a high fish intake at baseline; in the same section, an association between low habitual fish intake and accelerated spontaneous delivery was found in women who did not receive fish oil, whereas in women receiving fish oil the association seemed to be absent. The other section with singletons, the *current problems* trial (with women with suspected IUGR or threatening preeclampsia in the current pregnancy), was much smaller, with only 29, 47, and 28 women in strata defined by baseline fish intake, and the confidence limits around the estimates were correspondingly wide; this made it difficult to draw any strong conclusions regarding this particular type of women.

Strength of the present study was that the analyses accounted for elective delivery, which occurred in 40% of this high-risk population of pregnant women. The conclusions rest on the assumption of independent censoring. This means that women who have elective deliveries do not differ from the remaining women with respect to the (not

Table 2 European multicentre fish oil trial in pregnancy

Trial	*Baseline fish intake*	*Intervention group*	*Number of observations (N)*	*Proportion of elective deliveries (%)*	*Gestational age, hazard rate ratio (95% CI)*	
					Crude	*Adjusted*[a]
Previous problems	Low	Fish oil	58	32.8	0.58 (0.38, 0.89)	0.56 (0.36, 0.86)
		Olive oil	58	12.1	1 (ref.)	1 (ref.)
	Medium	Fish oil	101	32.7	0.61 (0.45, 0.84)	0.61 (0.44, 0.84)
		Olive oil	127	25.2	1 (ref.)	1 (ref.)
	High	Fish oil	67	22.4	0.93 (0.62, 1.40)	1.02 (0.67, 1.56)
		Olive oil	64	32.8	1 (ref.)	1 (ref.)
					Test for interaction[b] $P=0.20$	Test for interaction[b] $P=0.10$
Twins	Low	Fish oil	45	55.6	0.79 (0.43, 1.43)	0.79 (0.42, 1.46)
		Olive oil	41	43.9	1 (ref.)	1 (ref.)
	Medium	Fish oil	81	56.8	0.97 (0.60, 1.55)	0.95 (0.59, 1.54)
		Olive oil	89	60.7	1 (ref.)	1 (ref.)
	High	Fish oil	53	56.6	1.49 (0.81, 2.77)	1.46 (0.78, 2.72)
		Olive oil	47	61.7	1 (ref.)	1 (ref.)
					Test for interaction[b] $P=0.33$	Test for interaction[b] $P=0.36$
Current problems	Low	Fish oil	16	43.8	0.49 (0.19, 1.29)	0.45 (0.16, 1.30)
		Olive oil	13	38.5	1 (ref.)	1 (ref.)
	Medium	Fish oil	25	68.0	0.60 (0.25, 1.43)	0.72 (0.29, 1.82)
		Olive oil	22	36.4	1 (ref.)	1 (ref.)
	High	Fish oil	17	64.7	0.46 (0.13, 1.67)	0.39 (0.10, 1.58)
		Olive oil	11	63.6	1 (ref.)	1 (ref.)
					Test for interaction[b] $P=0.93$	Test for interaction[b] $P=0.72$

Abbreviation: CI, confidence interval.
Effect of fish oil supplementation, stratified by level of baseline fish intake. $n=935$ (sub-sample with information on fish intake at baseline, gestational age, and whether the delivery was spontaneous or elective). Shown are proportions of elective deliveries and gestational age hazard rate ratios (fish oil vs olive oil).
[a]Adjusted for maternal smoking (nonsmokers, 1–9 cigarettes per day, 10+ cigarettes per day), age (<20, 21–24, 25–29, 30–34, 35+ years), and parity. Based on slightly reduced data set with information on confounders ($n=927$).
[b]Test for interaction between baseline fish intake and intervention group.

observed) uncensored gestational age. The distinction between elective and spontaneous delivery may be difficult to make in practice, and the quality of this information could be a potential error source. However, in our study, the obstetrical data are likely to be of high quality as most of the participating 19 delivery wards were university obstetric departments. Also, a potential problem was that we did not have information on baseline fish intake for all women in the trial. There was however, no indication that the effects of fish oil on timing of delivery were different among women recruited before or after implementing the questions (Table 1). Another potential limitation of our study was that the study population consisted of high-risk pregnancies, and it is uncertain to what extent the findings can be generalised.

The patterns observed here in singletons are compatible with findings from our earlier trial with uncomplicated singleton pregnancies in which we solely saw an effect of fish oil supplementation on pregnancy duration in women with middle and low intake and no effect in women with high intake of fish (Olsen *et al*., 1992), and with some observational data, also from singleton pregnancies, suggesting that the direct associations noted in those studies between measures of exposure to dietary marine n-3 fatty acids and pregnancy duration might be limited to the low end of the exposure scale (Olsen *et al*., 1991; Olsen and Secher, 2002). In twin pregnancies, on the other hand, we found no effect of fish oil supplementation on timing of delivery, either in the overall analysis (Table 1, which we also reported earlier (Olsen *et al*., 2000)) or when we stratified according to baseline fish intake. The increased preterm risk in twin pregnancies may be caused by such factors as a greater physical distension of the uterus or a greater demand on the overall efficiency of the feto-maternal unit, which may overrule other determinants such as fish oil for the timing of spontaneous delivery.

The patterns observed in singletons could possibly explain discrepancies between some earlier trials in the field. It is possible that a large proportion of the women in some of these trials (e.g. the Norwegian trial (Helland *et al*., 2001)) have had a baseline intake above which no additional effect could be obtained with fish oil supplementation in the amounts given. The findings emphasise the need, whenever

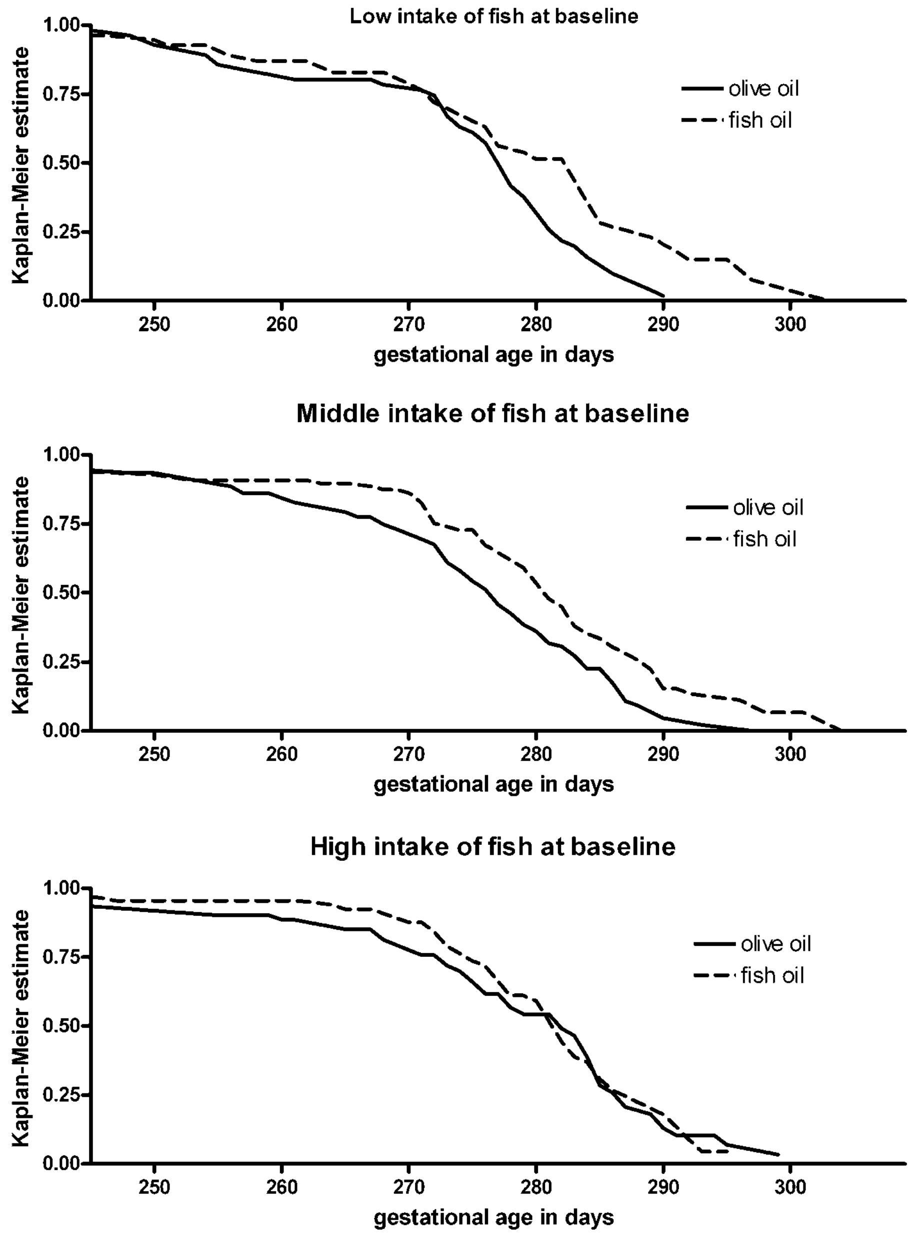

Figure 2 'Previous problems' trial. Kaplan–Meier survival curves. Survival time is the time of spontaneous delivery, and elective deliveries are considered censoring events. Stratified by intervention group (fish oil/olive oil) and baseline fish intake.

possible, to take baseline fish intake into account in future meta-analysis and uncritical pooling of estimates may result in dilution of effects.

If it is true that fish oil prolongs duration of pregnancy and that this effect depends on baseline fish intake, this would have potential implications for public health. Preterm delivery is a leading cause of perinatal mortality and morbidity, and preterm labour is an underlying factor for 85% of the deaths of normally formed babies. Considering the present data, however, any future recommendation to increase intake of *n*-3 fatty acids for the prevention of preterm birth should probably be given conditionally on the target group's fish consumption pattern. We did not have data to directly estimate the absolute amount of fish intake in women in the three strata, but data from similar studies may give some useful clues. During 1996–2002, general dietary patterns were assessed in approximately 70 000 pregnant women in the Danish National Birth Cohort (Olsen *et al*., 2006). When the algorithm used for defining low, middle, and high fish consumers in the present study was applied to the cohort data, we could estimate mean intake of fish at 16.3 g/day in the low fish group, 23.0 g/day

Table 3 European multicentre fish oil trial in pregnancy

Trial	*Intervention group*	*Baseline fish intake*	*Number of observations* (N)	*Gestational age, hazard rate ratio (95% CI)* Crude	*Gestational age, hazard rate ratio (95% CI)* Adjusted[a]
Previous problems	Fish oil	Low	58	1.00 (0.66, 1.52)	0.94 (0.61, 1.45)
		Medium	101	0.98 (0.68, 1.41)	0.92 (0.64, 1.33)
		High	67	1 (ref.)	1 (ref.)
	Olive oil	Low	58	1.60 (1.06, 2.41)	1.72 (1.12, 2.63)
		Medium	127	1.49 (1.03, 2.14)	1.55 (1.06, 2.25)
		High	64	1 (ref.)	1 (ref.)
Twins	Fish oil	Low	45	0.90 (0.50, 1.64)	0.80 (0.43, 1.46)
		Medium	81	0.70 (0.41, 1.20)	0.70 (0.41, 1.20)
		High	53	1 (ref.)	1 (ref.)
	Olive oil	Low	41	1.72 (0.93, 3.18)	1.48 (0.78, 2.81)
		Medium	89	1.09 (0.61, 1.92)	1.07 (0.60, 1.89)
		High	47	1 (ref.)	1 (ref.)
Current problems	Fish oil	Low	16	1.56 (0.55, 4.41)	1.59 (0.51, 4.98)
		Medium	25	1.09 (0.38, 3.17)	1.41 (0.45, 4.40)
		High	17	1 (ref.)	1 (ref.)
	Olive oil	Low	13	1.47 (0.44, 4.90)	1.40 (0.35, 5.65)
		Medium	22	0.85 (0.27, 2.62)	0.80 (0.23, 2.62)
		High	11	1 (ref.)	1 (ref.)

Abbreviation: CI, confidence interval.
Effect of baseline fish intake, stratified by trial and intervention group. $n=935$ (sub-sample with information on fish intake at baseline, gestational age, and whether the delivery was spontaneous or elective). Shown are gestational age hazard rate ratios (high baseline fish intake is the reference group).
[a]Adjusted for maternal smoking (nonsmokers, 1–9 cigarettes per day, 10+ cigarettes per day), age (<20, 21–24, 25–29, 30–34, 35+ years), and parity. Based on slightly reduced data set with information on confounders ($n=927$).

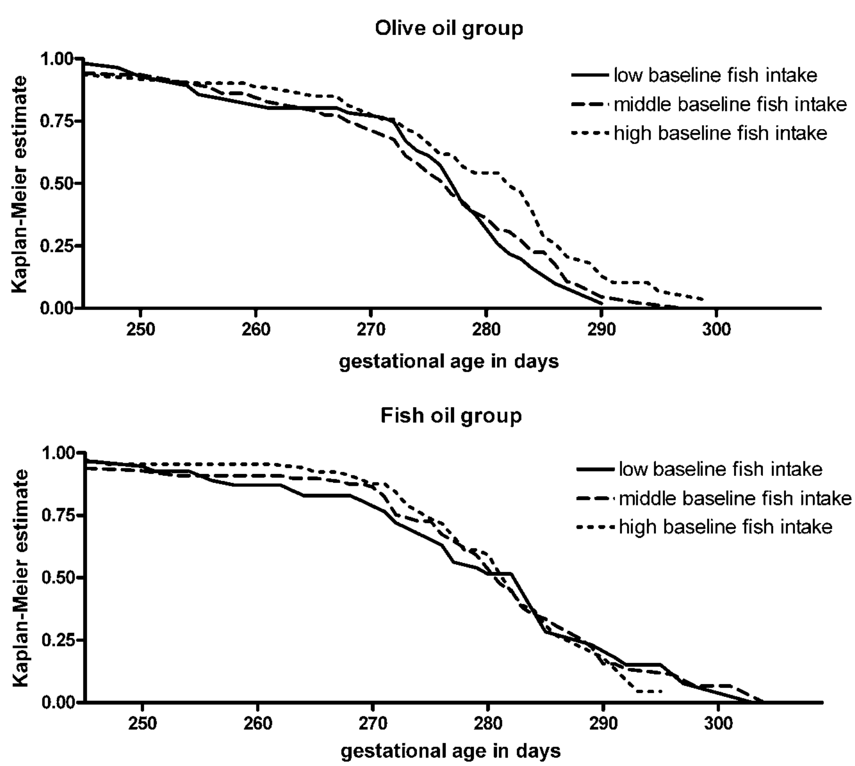

Figure 3 'Previous problems' trial. Kaplan–Meier survival curves. Survival time is the time of spontaneous delivery, and elective deliveries are considered censoring events. Stratified by baseline fish intake and intervention group (fish oil/olive oil).

Table 4 European multicentre fish oil trial in pregnancy

Trial	*Intervention group*	*Baseline olive oil intake*	*Number of observations* (N)	*Gestational age, hazard rate ratio (95% CI)*	
				Crude	*Adjusted*[a]
Previous problems	Fish oil	Low	110	0.88 (0.61, 1.27)	0.88 (0.61, 1.28)
		Medium	51	0.73 (0.47, 1.15)	0.78 (0.49, 1.22)
		High	65	1 (ref.)	1 (ref.)
	Olive oil	Low	124	0.91 (0.64, 1.28)	0.85 (0.59, 1.23)
		Medium	58	0.97 (0.64, 1.47)	0.92 (0.60, 1.39)
		High	66	1 (ref.)	1 (ref.)
Twins	Fish oil	Low	72	1.06 (0.64, 1.75)	1.08 (0.63, 1.82)
		Medium	45	0.82 (0.45, 1.50)	0.80 (0.43, 1.48)
		High	62	1 (ref.)	1 (ref.)
	Olive oil	Low	62	1.08 (0.64, 1.82)	0.99 (0.57, 1.69)
		Medium	46	0.95 (0.54, 1.69)	1.03 (0.58, 1.85)
		High	69	1 (ref.)	1 (ref.)
Current problems	Fish oil	Low	26	1.52 (0.57, 4.02)	2.11 (0.70, 6.36)
		Medium	11	1.65 (0.55, 4.95)	1.83 (0.52, 6.50)
		High	21	1 (ref.)	1 (ref.)
	Olive oil	Low	22	1.19 (0.50, 2.86)	0.70 (0.24, 2.08)
		Medium	5	1.08 (0.34, 3.48)	0.86 (0.25, 2.97)
		High	18	1 (ref.)	1 (ref.)

Abbreviation: CI, confidence interval.
Effect of baseline olive oil intake, stratified by trial and intervention group. $n=933$ (sub-sample with information on olive oil intake at baseline, gestational age, and whether the delivery was spontaneous or elective). Shown are gestational age hazard rate ratios (high baseline olive oil intake is the reference group).
[a]Adjusted for maternal smoking (nonsmokers, 1–9 cigarettes per day, 10 + cigarettes per day), age (<20, 21–24, 25–29, 30–34, 35 + years), and parity. Based on slightly reduced data set with information on confounders ($n=925$).

in the middle fish group, and 35.8 g/day in the high fish group.

However, an alternative explanation has been suggested. Findings of no effect of fish oil in some trials, using control regimens other than capsules with olive oil (Onwude *et al*., 1995; Helland *et al*., 2001; Knudsen *et al*., 2006), raised the possibility that the differences observed in this and our previous trial (Olsen *et al*., 1992, 2000), in length of gestation between groups of women receiving fish oil and olive oil, might indeed reflect a shortening effect of olive oil rather than a prolonging effect of fish oil (Olsen 2004). As habitual use of olive oil for cooking was recorded in the present trial (Olsen *et al*., 2000), we used the opportunity given here to examine whether this factor could be identified as a determinant of timing of delivery in this population. However, habitual use of olive oil was not associated with the hazard rate of spontaneous delivery, either among women who did or among those who did not receive fish oil supplements. Our data were only available at frequency level and did not allow us to quantify the absolute amount consumed of olive oil. We recognise this limitation. At least, we can conclude that a shortening effect of olive oil could not be substantiated in these data. We are not aware of any study which has indicated that populations consuming high amounts of olive oil, for example, Mediterranean populations, tend to have shorter gestations than other populations. Indeed, a recent randomised controlled trial seemed to indicate the opposite, as fewer preterm deliveries were observed in Norwegian women who adopted a Mediterranean-type diet during their pregnancy (Khoury *et al*., 2005). In our view, this is strong evidence against the possibility that a typical Mediterranean diet as such will lead to a shortening of gestation. Although this finding is not direct evidence regarding the impact of olive oil *per se*, it makes a substantial shortening effect of olive oil less credible.

In conclusion, earlier observations in singleton pregnancies that the prolonging effect of fish oil supplementation on timing of spontaneous delivery depends on the woman's fish intake were supported in the present study. Also, the study substantiated that a low habitual intake of fish is associated with accelerated spontaneous delivery, but our data could not substantiate that habitual use of olive oil for cooking could have such effect. We do recommend that baseline intake of fish be recorded in any future trials of effect of fish oil in pregnancy.

Acknowledgements

The study was funded by March of Dimes Birth Defects Foundation, Concerted Action (ERB-BMH1-CT92-1906), and PECO (ERB-CIPD-CT94-0235) programmes of the European Commission, and the Danish National Research Foundation. Lube Ltd provided Pikasol fish oil and olive oil capsules. The FOTIP Team is described in *British Journal of Obstetrics and Gynaecology* 2000; 107: 382–395.

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