Similar Effects on Infants of n-3 and n-6 Fatty Acids Supplementation to Pregnant and Lactating Women

Ingrid B. Helland, MD*‡; Ola Didrik Saugstad, MD, PhD‡; Lars Smith, PhD§; Kristin Saarem, PhD‖;
Kari Solvoll, PhD*; Trond Ganes, MD, PhD¶; and Christian A. Drevon, MD, PhD*

ABSTRACT. ***Objective.*** **There have been indications that high intake of n-3 long-chain polyunsaturated fatty acids (PUFAs) during pregnancy may increase birth weight and gestational length. In addition, n-3 long-chain PUFAs may be important for the neurobiological development of the infants. High levels of docosahexaenoic acid (DHA, 22:6 n-3) are found in the gray matter of the cerebral cortex and in the retina, and it seems as if the availability of long-chain PUFAs may be limiting cerebral development. The fetus and the newborn are dependent on a high supply from their mothers, either via the placenta or via breast milk. We supplemented pregnant and lactating women with n-3 or n-6 long-chain PUFAs to evaluate the effect on birth weight, gestational length, and infant development.**

Design. **We performed a double-blind, randomized study recruiting 590 pregnant, healthy, nulli- or primiparous women (19–35 years old) in weeks 17 to 19 of pregnancy. The women were provided 10 mL of either cod liver oil or corn oil daily until 3 months after delivery.**

Main outcome measures. **Primary outcomes were gestational length and birth weight. Electroencephalography (EEG) was done on the second day of life and at 3 months of age. Novelty preference (Fagan test) was used as an indicator of cognitive function at 6 and 9 months of age. The fatty acid pattern in umbilical plasma phospholipids and in breast milk was measured, and dietary assessments were performed, both on the mothers during pregnancy and on the infants at 3 months of age. The growth of the infants was followed up to 1 year of age.**

Results. **Three hundred forty-one mothers took part in the study until delivery. There were no significant differences in maternal body mass index before pregnancy and at birth, or parity between the 2 groups. Smoking habits and parental education were also similar in the 2 groups. The mean age of the mothers receiving cod liver oil was, by chance, 1 year higher than the age of the mothers receiving corn oil (28.6 [3.4] vs 27.6 [3.2] years). The maternal dietary intake in the 2 groups receiving cod liver oil or corn oil was similar, except for the supplementation. There were no differences in gestational length or birth weight between the cod liver oil group and the corn oil group (279.6 [9.2] vs 279.2 [9.3] days; 3609 [493] vs 3618 [527] g, respectively). Birth length, head circumference, and placental weight were also similar in the 2 groups. The concentrations of the n-3 fatty acids eicosapentaenoic acid (20:5 n-3), docosapentaenoic acid (22:5 n-3), and DHA in umbilical plasma phospholipids were higher in the cod liver oil group compared with the corn oil group (10.8 [7.6] vs 2.5 [1.8] μg/mL, 5.0 [2.6] vs 2.9 [1.3] μg/mL, 55.8 [20.6] vs 45.3 [12.8] μg/mL, respectively). Neonates with high concentration of DHA in umbilical plasma phospholipids (upper quartile) had longer gestational length than neonates with low concentration (lower quartile; 282.5 [8.5] vs 275.4 [9.3] days). No differences in EEG scores or Fagan scores were found, but neonates with mature EEG ($N = 70$) had a higher concentration of DHA in umbilical plasma phospholipids than neonates with immature EEG ($N = 51$) on the second day of life. Dietary information from 251 infants at 3 months of age was collected and 85% of these infants were exclusively breastfed, in addition to 12% who were partly breastfed. The breast milk of mothers supplemented with cod liver oil contained more n-3 long-chain PUFAs and less n-6 long-chain PUFAs than breast milk of mothers supplemented with corn oil. There were no significant differences in infant growth during the first year of life between the 2 groups.**

Conclusions. **This study shows neither harmful nor beneficial effects of maternal supplementation of long-chain n-3 PUFAs regarding pregnancy outcome, cognitive development, or growth, as compared with supplementation with n-6 fatty acids. However, it confirms that DHA concentration may be related to gestational length and cerebral maturation of the newborn.** ***Pediatrics*** **2001; 108(5). URL: http://www.pediatrics.org/cgi/content/full/108/5/e82;** ***dietary supplements, docosahexaenoic acid, arachidonic acid, gestational length, birth weight, infant, pregnancy, breastfeeding, cognitive functioning, electroencephalography.***

ABBREVIATIONS. PUFAs, polyunsaturated fatty acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; AA, arachidonic acid; EEG, electroencephalography; SD, standard deviation; DPA, docosapentaenoic acid.

Considerable attention has been paid to the effect of long-chain n-3 polyunsaturated fatty acids (PUFAs) on pregnancy outcome. Some authors have suggested that high consumption of docosahexaenoic acid (DHA, 22:6 n-3) and eicosapentaenoic acid (EPA, 20:5 n-3) from fish and fish oils may increase birth weight and lower the risk of early delivery and preeclampsia. These hypotheses arose from epidemiologic observations of longer gestation, larger infants, and perhaps a reduced incidence of preeclampsia in areas with high fish intake.[1,2] Inde-

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From the *Institute for Nutrition Research, ‡Department of Pediatric Research, and §Institute of Psychology, University of Oslo, Oslo; ‖Peter Möller, Avd Orkla ASA; and ¶Department of Neurology, The National Hospital, Oslo, Norway.

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Address correspondence to Ingrid B. Helland, MD, Institute for Nutrition Research, University of Oslo, Box 1046 Blindern, N-0316 Oslo, Norway. E-mail: i.b.helland@basalmed.uio.no

pendent of their possible effects on the duration of pregnancy, fetal growth, and preeclampsia, long-chain n-3 and n-6 fatty acids may also be beneficial for the development of infants. High levels of DHA are found in the gray matter of the cerebral cortex, and in the photoreceptor outer segment membranes of the retina.[3] In the fetus, long-chain PUFAs are preferentially accumulated in the brain during the last trimester of pregnancy and the first months of life.[4] Data obtained with stable isotopes show that preterm as well as term infants can convert linoleic acid (18:2 n-6) and α-linolenic acid (18:3 n-3), respectively, to arachidonic acid (AA, 20:4 n-6) and DHA.[5–7] Despite this, desaturation enzyme systems in the human fetal liver seem to be immature and unable to supply sufficient long-chain PUFAs to meet the requirements until 16 weeks after birth.[8] The capacity of the placenta to synthesize long-chain PUFAs from essential fatty acids is very limited, but there is an active transport of long-chain PUFAs across the placenta, as shown by a maternal-fetal concentration gradient of long-chain PUFAs in favor of the fetus.[9] A placental plasma membrane fatty acid binding protein has also been identified, which binds long-chain PUFAs with a preference for DHA and AA.[10–13] Moreover, maternal long-chain PUFA status during pregnancy is critical for the essential fatty acid status in the newborn.[14,15] Postmortem studies of fetuses, stillbirths, and preterm infants have shown fetal accretion of ~70-mg n-3 long-chain PUFAs per day during the last trimester, most of which is DHA.[4,16]

Breast milk contains a variety of long-chain PUFAs, including DHA. Infants can be exposed to a wide range of DHA levels in breast milk, depending primarily on maternal dietary intake. The concentration of DHA in human milk varies from as low as 0.1% to 1.4% in populations where fish consumption is high.[17] Supplementation of lactating women with fish oil or cod liver oil increases the DHA content of their milk and of their plasma phospholipids.[18–20] Furthermore, several authors have reported that children who were breastfed as infants had superior psychomotoric development compared with those who were formula-fed.[21–24] This has been related to the presence of DHA in breast milk, a fatty acid not included in most formulas. The association between dietary DHA and improved retinal and neural outcomes has been verified in randomized trials involving term as well as preterm infants.[25–28] However, we do not know the optimal dose of DHA for fetal and infant growth and health.

The intake of marine n-3 fatty acids is relatively high in Norway, as compared with other countries.[29,30] The pregnant and lactating mothers have a high concentration of DHA in plasma phospholipids and breast milk,[20] and a great majority of the Norwegian mothers also breastfeed their infants up to at least 3 months after giving birth,[31] thus providing their infants with preformed DHA.

The aim of this study was to investigate whether dietary supplementation of long-chain n-3 fatty acids to pregnant and lactating Norwegian mothers would affect gestational length, birth weight, and the biochemical status of the neonates. Electroencephalography (EEG) was analyzed in the neonatal period and again at 3 months of age. Novelty preference was used as an indicator of cognitive functioning at 6 and 9 months after birth.

MATERIALS AND METHODS

Study Design

Pregnant women were enrolled between December 1994 and October 1996 at the National Hospital and Baerum Central Hospital in the Oslo area. Primary outcomes were gestational length and birth weight (Table 1). Secondary outcomes were birth length, head circumference, and fatty acid patterns in umbilical plasma phospholipids and in breast milk. EEG was done on the second day of life and at 3 months of age as a measure of brain maturity, and cognitive tests were performed at 6 and 9 months of age (Table 1, Fig 1). From previous data,[32] we calculated that we needed 400 participants in the study, 200 in each group. (A difference in gestational age of 4 days and standard deviation [SD] = 13, $N = 167$ in each group; a difference in birth weight of 150 g, SD = 528, $N = 196$; $\alpha = 5\%$, $\beta = 20\%$.)

Five hundred ninety pregnant women were enrolled at the first routine ultrasound scan examination at week 17 to 19 of pregnancy (Fig 2). Inclusion criteria were healthy women with single pregnancies between 19 and 35 years of age, and nulli- or primipara (Table 1). The women should intend to breastfeed their infants, and none of the participants should have taken any supplements of n-3 fatty acids earlier during the pregnancy. Exclusion criteria were premature births, birth asphyxia, infections, and anomalies in the infants that required special attention.

The participants randomly received either 10 mL/day of cod liver oil (Peter Möller, Avd Orkla ASA, Oslo, Norway), or 10 mL/day of corn oil (Table 2). The amount of fat-soluble vitamins was identical in the 2 oils, 117 μg/mL of vitamin A, 1 μg/mL of vitamin D, and 1.4 mg/mL of dl-α-tocopherol. The women continued taking the supplements until 3 months after delivery (Fig 1). According to the Norwegian guidelines of infant nutrition, 5 mL of cod liver oil daily is recommended for infants from 4 weeks of age.

The study was randomized and double-blinded, and the randomization was performed by a computer program. The participants received written information and consented to participate in the study, which was approved by the regional ethics committee.

Information about the mothers was collected from pregnancy records and from food frequency questionnaires. Birth data and data of the infants were collected from birth records and information given by the mothers via questionnaires.

Blood and Milk Sampling

Blood samples were taken from the mothers when entering the study in week 18 and in week 35 (Fig 1) in ethylenediaminetetraacetic acid-containing vacuum-tubes, and plasma was kept at −70°C under nitrogen. Blood samples were also collected from the

TABLE 1. Inclusion Criteria and Primary and Secondary Outcomes

Inclusion criteria
  Healthy women with single pregnancies between 19 and 35 years of age
  Nulli- or primiparous
  Intention to breastfeed their infant
  No supplement of n-3 long-chain PUFAs earlier during the pregnancy
Primary outcomes
  Gestational length
  Birth weight
Secondary outcomes
  Head circumference
  Fatty acid pattern in umbilical plasma and breast milk
  EEG maturity
  Cognitive function (Fagan Test of Intelligence)
  Growth during first year of life

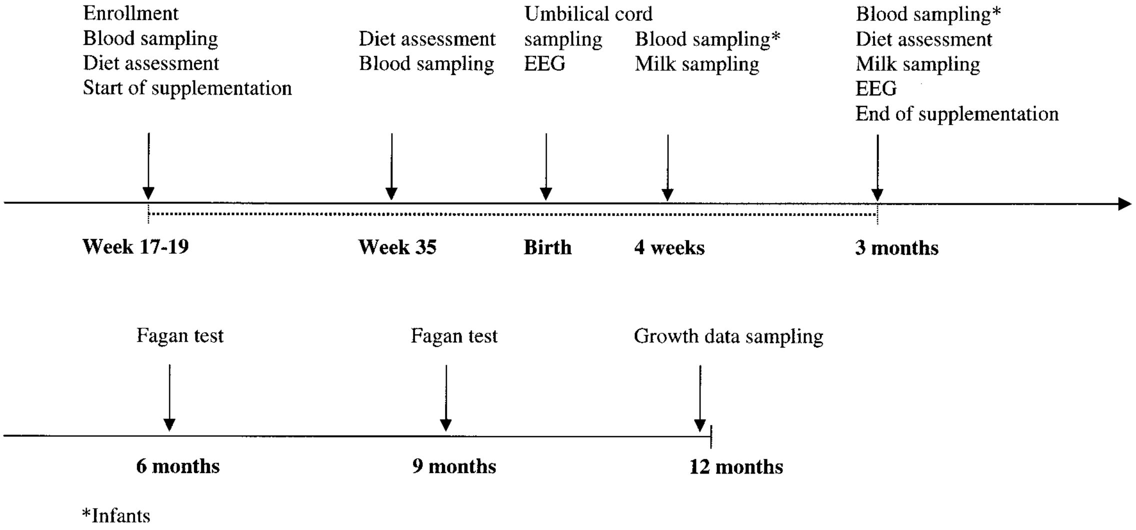

Fig 1. Design of the study.

umbilical cords, and from the infants when they were 4 and 13 weeks old (Fig 1).

Milk samples were collected at 4 and 13 weeks after birth. The samples were taken from a morning feed (never the first one), 3 to 5 minutes after the infant started suckling. The samples were collected the day before they were provided to the hospital and were kept in a home refrigerator until the next day when they were frozen at −70°C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 μg/mL, respectively.

Growth Recordings

All infants were routinely weighed and measured at local health care centers, and the mothers copied the records and mailed the data to the authors. Recumbent length was measured as the child lay on a firm table with a measuring stick fastened. The head was held firmly against a fixed upright placed at the zero mark. A movable upright crossed the table above the soles of the feet and was brought firmly against the soles.

Diet Evaluation

All participating mothers filled in a self-administered food frequency questionnaire when they entered the study (week 18) and at week 35 of pregnancy. The questionnaire has been validated by comparing it with weighed diet records in elderly women,[33] dermatological outpatients by 48-hour recall interviews,[34] and against the fatty acid pattern of plasma phospholipids in 579 adult subjects, demonstrating that the questionnaire may be used for estimation of dietary intake of very long-chain n-3 fatty acids.[35] The mothers were asked to continue their habitual diet during the study period.

When the infants were 3 months old, the mothers answered a questionnaire covering the infants' usual diet. This included questions about breastfeeding and supplements of cod liver oil given to the infants.

Analytical Methods

The content of fatty acids in plasma phospholipids and in breast milk was determined by gas liquid chromatography.[20,36] Analyses of breast milk were performed on subjects where blood samples from the infant were available. Total lipid concentration in milk was calculated based on the peak areas of methyl esters relative to the internal standard.[36]

EEG

All of the included neonates born at The National Hospital were scheduled for EEG on their second day of life and at 3 months of age.

The EEG recordings were performed on a Medelec digital EEG machine (DG Discovery, Medelec, Vickers Medical, England). The 10 scalp electrodes were placed according to a modified international 10–20 system.[37] The EEG records were analyzed blinded by an experienced clinical neurophysiologist (T.G.) for frequency and amplitude distributions, as well as for specific changes related to sleep and prematurity.[38] Based on these data, each EEG record was given a maturity score from 1 to 3. EEG classified as 1 had no prematurity signs and a full-term frequency and amplitude pattern. EEG classified as 3 had clearly premature signs such as brushes, encoches frontales, slow background activity during wakefulness, hemispheric a synchrony and periods of trace alternant sleep with hemispheric a synchrony and intermittent activity pattern. EEG classified as 2 had some premature signs.[39]

Assessment of Cognitive Functioning

The participants were assessed by one of the authors (L.S.) administering the Fagan Test of Infant Intelligence at 27 and 39 weeks of age.[40] The Fagan Test of Infant Intelligence is a paired comparison test of visual novelty preference. The participants received 10 novelty problems on both occasions, and all problems involved comparisons of photographs of faces. Each problem consisted of a brief familiarization with one target, then pairing the briefly studied pattern with a picture of a new face. All problems involved comparisons of digitized face images presented on a computer monitor. Novelty preferences were measured by differential fixation to the novel over the previously seen facial pattern. Infants typically devote a greater percentage of total fixation to the novel target. At both ages, identical targets were used, but study and test times were shorter at 39 weeks than at 27 weeks. To increase the reliability, the test scores at both time points were combined.

Statistics

Data are presented as means and standard deviation. A 2-tailed Student *t* test was used to examine differences between supplementation groups for continuous variables. χ^2 test was used for categorical values. A P value <.05 was considered significant. SPSS for Macintosh 6.1.1. (SPSS Inc, Chicago, IL) was used for calculations.

RESULTS

Baseline Characteristics of Mothers

There were no differences in maternal age, body mass index before pregnancy, body mass index at birth, parity, smoking, or maternal or paternal education between the 2 randomized groups among participating mothers. Out of the 590 recruited, 27 mothers/infants were excluded because of 1 stillbirth (the

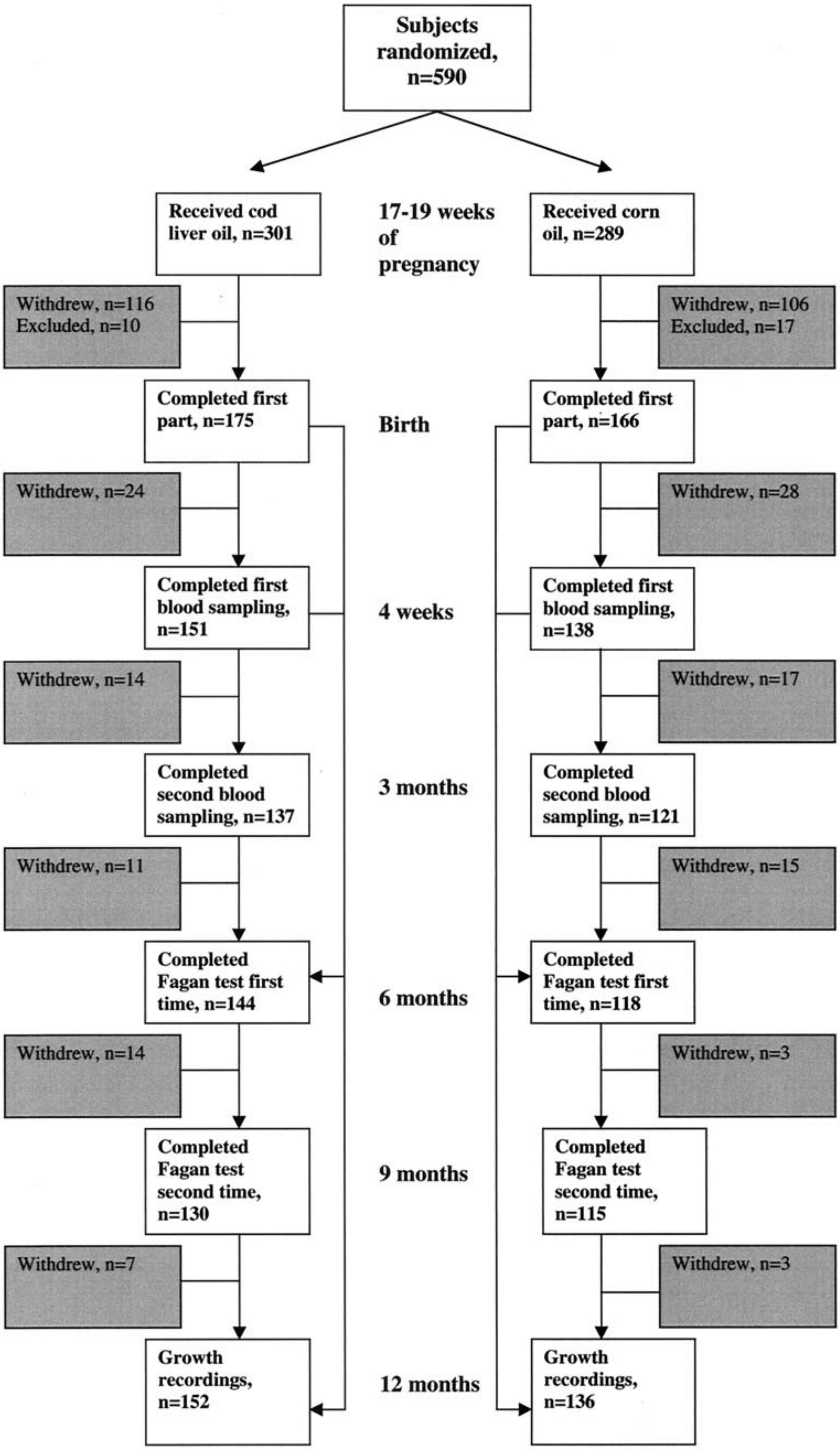

Fig 2. Trial profile summarizing participant flow, numbers of randomization assignment, interventions, and measurements for each randomized group.

mother had hereditary angioneurotic syndrome, received cod liver oil), 2 miscarriages (week 20 and 21, 1 in each group), 3 premature births (1 in the cod liver oil group and 2 in the corn oil group), 7 infants had anomalies (1 had diaphragmatic hernia, 1 atresia of the vagina [died after 2 days], 1 multiple anoma-

TABLE 2. Content of Fatty Acids in Cod Liver Oil and Corn Oil (mg/10 mL)

Fatty Acid	Cod Liver Oil	Corn Oil
14:0	320	0
16:0	775	848
Sum 16:1	650	0
18:0	161	148
18:1 n-9	1340	2373
Sum 18:1	1717	2419
18:2n-6	160	4747
18:3n-3	75	92
18:4n-3	230	0
20:1	1185	33.3
20:2n-6	23.3	0
20:4n-6	27.5	0
20:4n-3	56.6	0
20:5n-3	803	0
21:5n-3	35.0	0
Sum 22:1	569	0
22:4n-6	24.1	0
22:5n-3	112	0
22:6n-3	1183	8.3
24:1n-9	22.5	0
Sum n-3*	2632	350
Sum n-6	235	4747
Cholesterol (mg)	41.6	0

* Includes all identified n-3 fatty acids.

lies that led to death, 1 ventricular septum defect, 1 coarctation of the aorta, 1 transposition of the great arteries and ventricular septum defect, and 1 had cleft palate; 3 belonged to the cod liver oil group and 4 to the corn oil group), 11 infants had infections/sepsis (4 in the cod liver oil group and 7 in the corn oil group), 1 had birth asphyxia (clinical signs of hypoxic ischemic encephalopathy and increased levels of plasma liver transaminases and creatinine, belonged to the cod liver oil group), 1 was excluded because of maternal toxoplasmosis infection during pregnancy (corn oil group), and 1 received both cod liver oil and corn oil by mistake (corn oil group). In addition, 222 women withdrew before giving birth. The participants were free to withdraw without giving a reason, but we received information from about 50%. Most of the women who withdrew did so because of feeling discomfort taking the oil (43.1% and 38.7% in the cod liver oil group and corn oil group, respectively) or lack of compliance (9.5% in the cod liver oil group and 16.1% in the corn oil group; Fig 2). The remaining 341 women are described in Table 3. The mean age of the mothers receiving cod liver oil was, by chance, 1 year higher than the age of the mothers receiving corn oil ($P \leq .01$; Table 3).

Maternal Diet

There were no significant differences in dietary intake of nutrients between the groups receiving cod liver oil or corn oil at baseline (Table 4). At 35 weeks of pregnancy, the differences between the groups reflected different supplementation (cod liver oil or corn oil).

Fatty Acid Pattern in Plasma Phospholipids and Anthropometric Data

There was no difference between the 2 groups in maternal plasma phospholipids concentration of DHA before entering the study (94.7 [22.5] vs 94.5 [21.8] μg/mL). After 4 months of supplementation, the concentration of DHA was significantly higher in the cod liver oil group than in the corn oil group (147.2 [34.1] vs 101.8 [25.9] μg/mL).

The concentrations of the n-3 fatty acids EPA, docosapentaenoic acid (DPA, 22:5), and DHA in umbilical plasma phospholipids were higher in the cod liver oil group as compared with the corn oil group (432%, 172%, and 123%, respectively), whereas the concentrations of the n-6 fatty acids AA and DPA were higher in the corn oil group (128% and 225%, respectively; Table 5).

There were no differences in gestational length or birth weight between the 2 supplementation groups (Table 6). Birth length, head circumference, and placental weight were also similar in the 2 groups. Also, when the excluded infants were included in the statistical analyses, no differences were found between the 2 groups. Estimated blood loss was similar in the 2 groups. The cesarean section rate was higher in the cod liver oil group as compared with the corn oil group (Table 6). There were, by chance, 7 breech deliveries in the cod liver oil group, whereas there was none in the corn oil group prompting the use of elective cesarean section. Four labors in the cod liver oil group and 6 in the corn oil group were induced because of overtime. When we compared the quartile with the highest concentration of DHA in umbilical plasma phospholipids with the quartile with the lowest concentration of DHA, we found significantly

TABLE 3. Characteristics of Mothers Completing the Study Until Giving Birth (Mean [SD])

	Cod Liver Oil	*n*	Corn Oil	*n*
Age (y)	28.6 (3.4)	175	27.6 (3.2)**	166
BMI before pregnancy (kg/m^2)	22.2 (2.9)	141	22.5 (3.3)	125
BMI at birth (kg/m^2)	28.0 (3.5)	156	28.5 (4.1)	153
Parity	0.3 (0.5)	174	0.3 (0.5)	164
Smoking (%)	16	162	22	156
Education		173		164
<10 y (%)	2.9		1.8	
10–12 y (%)	21.4		31.1	
>12 y (%)	75.7		67.1	
Education of partner		165		161
<10 y (%)	6.1		1.9	
10–12 y (%)	23.6		24.8	
>12 y (%)	70.3		73.3	

BMI indicates body mass index.

** $P < .01$.

TABLE 4. Daily Intake of Energy and Nutrients as Evaluated by a Food Frequency Questionnaire (Mean [SD])

	Week 18		Week 35	
	Cod Liver Oil ($n = 171$)	Corn Oil ($n = 159$)	Cod Liver Oil ($n = 137$)	Corn Oil ($n = 134$)
Energy (MJ)	8.2 (2.0)	8.2 (2.0)	8.7 (2.3)	8.6 (2.2)
Protein (g)	76.7 (18.1)	75.5 (17.7)	76.5 (19.2)	74.2 (17.9)
Fat (g)	68.2 (20.2)	67.6 (22.1)	76.0 (26.4)	76.8 (26.5)
Carbohydrate fiber (g)	257 (69)	258 (67)	267 (75)	263 (69)
Sugar (g)	50.6 (37.4)	53.5 (33.0)	58.8 (39.5)	61.0 (37.7)
Alcohol (g)	1.7 (3.1)	1.5 (3.0)	0.6 (1.2)	0.8 (1.9)
Fiber (g)	20.4 (5.4)	20.0 (6.2)	20.2 (6.1)	18.9 (5.5)
Cholesterol (mg)	253 (76)	250 (76)	280 (85)	241 (85)***
Saturates (g)	27.2 (8.4)	27.1 (9.5)	28.3 (10.5)	28.2 (10.8)
Monoenes (g)	23.8 (7.2)	23.7 (7.8)	27.4 (8.7)	26.2 (9.2)
Polyenes (g)	12.1 (4.5)	11.8 (4.7)	14.4 (7.1)	16.7 (6.1)**
18:2 n-6	9.3 (3.8)	9.1 (3.9)	9.4 (6.1)	14.2 (5.2)***
18:3 n-3	1.3 (0.5)	1.2 (0.5)	1.3 (0.9)	1.4 (0.7)
20:4 n-6	0.1 (0.05)	0.1 (0.04)	0.1 (0.04)	0.1 (0.03)***
20:5 n-3	0.2 (0.2)	0.2 (0.2)	0.9 (0.09)	0.1 (0.1)***
22:5 n-3	0.05 (0.03)	0.05 (0.03)	0.2 (0.02)	0.04 (0.02)**
22:6 n-3	0.3 (0.3)	0.3 (0.3)	1.4 (0.1)	0.2 (0.2)***
Retinol (eq mg)	1.7 (0.9)	1.6 (0.8)	2.5 (0.9)	2.4 (0.6)
β-Carotene (mg)	3.4 (2.5)	3.3 (2.1)	3.6 (3.5)	3.3 (2.2)
Tocopherol (mg)	8.6 (3.8)	9.5 (8.4)	18.9 (1.7)	19.0 (1.7)
Vitamin D (μg)	8.4 (5.2)	8.0 (6.8)	13.2 (1.8)	13.4 (1.8)

** $P < .01$, *** $P < .001$ compared with values for the cod liver oil group.

TABLE 5. Fatty Acids (μg/mL) in Umbilical Plasma Phospholipids (Mean [SD])

Fatty Acids	Cod Liver Oil ($n = 148$)	Corn Oil ($n = 137$)
20:3 n-9	2.3 (1.5)	2.5 (1.6)
Σn-6	156.3 (55.4)	176.3 (35.5)***
20:4n-6	69.5 (17.3)	89.1 (18.4)***
22:5n-6	1.6 (0.9)	3.6 (1.5)***
Σn-3	73.7 (30.0)	52.0 (14.9)***
20:5n-3	10.8 (7.6)	2.5 (1.8)***
22:5n-3	5.0 (2.6)	2.9 (1.3)***
22:6n-3	55.8 (20.6)	45.3 (12.8)***
Σn-3/Σn-6	0.5 (0.1)	0.3 (0.1)***

*** $P < .001$ compared with group values for the cod liver oil.

TABLE 6. Anthropometric Birth Data From Groups Receiving Cod Liver Oil or Corn Oil (Mean [SD])

	Cod Liver Oil ($n = 175$)	Corn Oil ($n = 166$)
Gestational length (d)	279.6 (9.2)	279.2 (9.3)
Weight (g)	3609 (493)	3618 (527)
Length (cm)	50.7 (2.0)	50.8 (2.2)
Head circumference (cm)	35.3 (1.5)	35.2 (1.6)
Placental weight (g)	652 (131)	652 (137)
Blood loss (mL)	362 (219)	354 (324)
Induced labors (n)	20	11
Cesarean section (n)	28	14*
Elective (n)	11	2**
Acute (n)	17	12
Boys/girls	82/93	84/82

* $P \leq .05$, ** $P \leq .01$ compared with values for the cod liver oil group.

longer gestational length (282.5 [8.5] vs 275.4 [9.3] days, $P < .001$) in the group with the higher DHA concentration, but no differences in birth weight, birth length, or head circumference.

We received growth records from 288 infants; 152 in the cod liver oil group and 136 in the corn oil group. At no time points were there any differences in weight, length, or head circumference between the 2 supplementation groups from birth to 12 months of age (Fig 3).

Diet and Fatty Acid Pattern in Breast Milk

We received dietary information from 251 infants from whom we had blood samples. At 3 months of age, 213 infants were exclusively breastfed in addition to 29 infants who were partly breastfed. Supplement of cod liver oil was given to 130 infants.

The content of AA, EPA, DPA n-3, and DHA in breast milk 4 weeks and 3 months after birth is illustrated in Table 7. AA was significantly higher in the corn oil group (107% and 112% at 4 weeks and 3 months after birth, respectively), whereas n-3 long-chain fatty acids were significantly higher in the cod liver oil group (EPA 331% and 273%, DPA n-3 189% and 174%, and DHA 280% and 255% at 4 weeks and 3 months after birth, respectively).

EEG Analyses

Of the infants born at the National Hospital, 181 neonates fulfilled the criteria for EEG analyses: 86 in the cod liver oil group and 95 in the corn oil group. We have EEGs from 149 neonates—66 in the cod liver oil group and 83 in the corn oil group, and from 122 infants three months old (61 in both groups). One of the EEGs in the corn oil group at second day of life was excluded from additional analyses because of signs of pathology. There were no differences between the groups in maturity as evaluated from the EEGs, neither at day 1 nor at 3 months of age (Table 8).

Between neonates with mature (score 1; $N = 70$) and immature EEG scores (score 2 and 3; $N = 51$), there were significant differences in umbilical plasma phospholipid levels of EPA (7.9 [9.0] vs 5.1 [4.5] μg/mL, $P = .03$), DPA n-3 (4.6 [2.8] vs 3.3 [1.5]

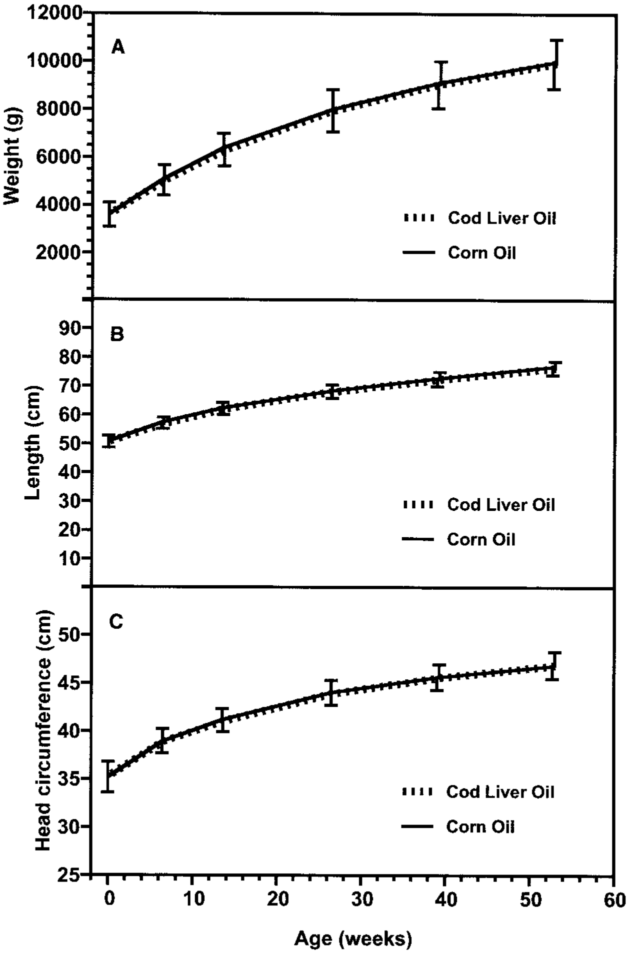

Fig 3. Growth in infants of mothers receiving cod liver oil or corn oil during second half of pregnancy and the first 3 months after birth. Weight (panel A), length (panel B), and head circumference (panel C) were measured at 6 weeks, and at 3, 6, 9, and 12 months after birth. At no time points were there any differences between the 2 groups.

μg/mL, P = .003) and DHA (55.0 [20.7] vs 46.5 [10.8] μg/mL, P = .004) at second day of life. At 3 months of age, there were no significant differences in plasma phospholipid levels between those with mature and immature EEGs (data not shown).

Assessment of Cognitive Functioning

There were no differences in novelty preference between the cod liver oil group and the corn oil group, neither at 6 (55.2 [4.5] vs 55.4 [3.7] %) nor at 9 months of age (55.5 [3.8] vs 56.2 [3.5] %). When the scores from 6 and 9 months of age were combined, there still was no difference between the 2 groups. When infants with high DHA concentration in umbilical plasma phospholipids (upper quartile) were compared with infants with low concentration of DHA (lower quartile), there were no differences in novelty preference. Neither did we find differences in DHA concentrations between infants with high novelty preference (upper quartile) and low novelty preference (lower quartile).

DISCUSSION

We did not detect any effect of maternal dietary supplementation with long chain n-3 fatty acids on gestational length or birth weight, as compared with dietary supplementation with n-6 fatty acids. However, we observed that neonates with high concentration of DHA in umbilical plasma phospholipids had higher gestational age than neonates with low concentration of DHA. Earlier reports have been conflicting. A study on n-3 fatty acid supplementation prophylaxis in high-risk pregnancies found no effect of maternal supplementation with n-3 fatty acids on intrauterine growth retardation and gestational length compared with no supplementation.[41] A randomized clinical trial of fish oil supplementation in high-risk pregnancies showed that fish oil supplementation reduced the recurrence risk of preterm delivery, but had no effect on intrauterine growth retardation and pregnancy-induced hypertension.[42] The control group received olive oil, with the assumption that olive oil is inert in relation to the variables studied. Another study showed that supplementation of healthy pregnant women with fish oil resulted in prolonged gestation by 4 days and increased birth weight by 107 g, as compared with supplementation with olive oil.[32] However, in this latter study, the authors did not find any difference in gestational length or birth weight when fish oil supplementation was compared with unsupplemented women. It has been speculated that the unsupplemented women increased their fish consumption, but it is also possible that olive oil has effects so far unreported. In our study, we registered diet twice during pregnancy and there was no increase in fish consumption in any of the groups.

This study was performed on a population with normal birth weight and gestational age. Before starting the study, we did statistical analyses based on a Danish material,[32] to calculate the numbers of participants necessary to detect differences in gestational age and birth weight. Performing the study on a population with low birth weight and gestational age may have increased the chances of detecting effects of supplements with long-chain n-3 PUFAs.

To our knowledge, this is the first study investigating the effect of supplementing mothers during pregnancy and lactation with n-3 long-chain PUFAs on subsequent child development. The Fagan test of infant cognitive function is predictive for IQ at older age (correlation: 0.40–0.50, range: 0.25–0.66), which is comparable to the Bayley test.[40] We detected no difference in novelty preference between the 2 supplementation groups, neither at 6 nor at 9 months of age. A difference of 3 points would have been considered clinically significant, and the study has statistical power to detect such a difference. However, it is possible that a small difference that is too small to be detected early in life will increase, as the children grow older. Additional follow-ups may, therefore, be of importance and more detailed testing at later ages is underway to explore whether more subtle or specific differences in neurodevelopmental performance can be discerned. Several studies have investigated the effect of supplementing formula with long-chain PUFAs on mental development.[27,28,43–46] The results have been inconsistent and inconclusive, as reported by Simmer.[47] The conflicting results can be attribut-

TABLE 7. Fatty Acids in Breast Milk (wt%) 4 Weeks and 3 Months After Birth

Fatty Acids	4 Weeks		3 Months	
	Cod Liver Oil (n = 145)	Corn Oil (n = 138)	Cod Liver Oil (n = 122)	Corn Oil (n = 111)
20:4 n-6	0.38 (0.07)	0.41 (0.07)***	0.33 (0.06)	0.37 (0.09)***
20:5 n-3	0.43 (0.19)	0.13 (0.09)***	0.41 (0.22)	0.15 (0.13)***
22:5 n-3	0.36 (0.13)	0.19 (0.09)***	0.33 (0.12)	0.19 (0.09)***
22:6 n-3	1.37 (0.58)	0.49 (0.32)***	1.20 (0.57)	0.47 (0.40)***
Total lipid	4.05 (1.55)	4.40 (1.43)	3.80 (1.71)	3.99 (1.68)

*** $P \leq .001$ compared with mean values for the cod liver oil group.
The total lipid content is in mg/100 μL.

TABLE 8. EEG Scores at 1 Day and 3 Months of Age*

	1 Day		3 Months	
	Cod Liver Oil	Corn Oil	Cod Liver Oil	Corn Oil
Mature	37	50	56	58
Lightly immature	22	21	3	2
Immature	7	11	2	1

* The number given different scores is presented for each group.

able to differences in dosage, duration of supplementation, different long-chain PUFA preparations (fish oil, single-cell oil), and different control formulas. In contrast to these studies, where the neonates and infants received different formulas, 95% of the infants in our study received breast milk until 3 months of age. All breast milk contains both AA and DHA, and the difference between the groups is a difference in dosage of these dietary fatty acids. Gibson et al[48] supplemented lactating women from day 5 to 12 weeks after birth with single-cell oil DHA, and found that supplementation of DHA may be positively related with Bayley's Mental Development Indices at 1 year of age. However, at 2 years of age, no associations were found. Breast milk seems to be superior to formula in relation to cognitive development,[21,49] and the presence of long-chain PUFAs in breast milk and not in formula, has been suggested as an explanation. However, in addition to long-chain PUFAs, breast milk contains a number of other constituents (β-carotene, nucleotides, cholesterol, hormones, globulines, etc) that in addition to or instead of AA and DHA might explain the better outcome of breastfed infants as compared with formula-fed infants.

EEG represents spontaneous electrical waves mainly reflecting synaptic activity in the cerebral cortex.[37] The phylogenetic and ontogenetic changes seen in the EEG patterns reflect the evolution and development of the cerebral cortex with increasing complexity and magnitude of the intracortical organization.[38] Experimental data suggest that cortical functional activity as well as the number of intracortical synaptic connections can be influenced by a variety of factors including enhanced use, stimulating environments, toxic factors, and (mal-) nutrition.[38] Whether single nutrients such as DHA can influence cerebral maturation is still unclear, but in our study no difference was demonstrated in the EEG maturity scores between the 2 supplementation groups. However, it should be noted that the neonatal group with mature EEG had higher concentration of DHA in the umbilical plasma phospholipids as compared with neonates with more immature EEGs.

Early trials of n-3 long-chain PUFA supplementation of preterm neonates have suggested an influence on growth.[50–52] A reduction in growth in term infants supplemented with different forms of long-chain n-3 fatty acids has never been shown.[43,45,53] This is in accordance with our results, where no significant difference was seen between the groups supplemented with cod liver oil or corn oil.

As expected, fatty acid pattern in umbilical plasma phospholipids was greatly influenced by the supplementation given to the mothers, in accordance with other studies.[15,54]

The mothers' intake of cod liver oil or corn oil also greatly influenced the fatty acid pattern in their breast milk. Mothers receiving corn oil had higher levels of AA in their breast milk than mothers receiving cod liver oil did. It has earlier been shown that maternal intake of single-cell oil or cod liver oil do not affect the amount of AA in the breast milk.[20,55] The higher concentration of AA in breast milk of corn oil supplemented mothers is most probably caused by the increased intake of linoleic acid and thereby increased concentration of AA in maternal plasma (data not shown).

The intake of n-3 very long-chain PUFAs (EPA+DPA+DHA) before supplementation(550 mg/day), was higher than for lactating women in the United States (121 mg/day).[19] In contrast, the intake of n-6 PUFAs before supplementation with corn oil was below what has been found in other countries. After supplementation, the intake of n-6 PUFAs was in the same range as reported in other populations.[29,56] In Norway, >90% of the mothers breastfeed their infants,[31] in contrast to only 66% in England[57] and 60% in the United States.[58] Breast milk of Norwegian mothers contain more DHA than breast milk of mothers from other parts of the world.[18,19,55,59,60] It could be that by performing this study on a population with low intake of DHA, supplementation with cod liver oil during pregnancy and lactation would lead to different results. It is also possible that supplementation during pregnancy of a population that did not intend to breastfeed their infants, would have other consequences.

CONCLUSION

This study on Norwegian mothers shows neither clear beneficial nor harmful effects of maternal supplementation of n-3 long-chain PUFAs regarding gestational length, birth weight, cognitive development, or growth, as compared with supplementation with n-6 fatty acids. Both DHA and AA are important for fetal and infant development[4,26,61,62] and these fatty acids are considered essential for the newborn infant.[8,63] It is possible that by studying supplements raising the concentration of either AA or DHA, we have compared groups receiving 2 different beneficial supplements.

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