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Original article

Does intravenous fish oil affect the growth of extremely low birth weight preterm infants on parenteral nutrition?

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SUMMARY

Background & aims: Long chain n-3 fatty acids (n-3 LCPUFA) play a pivotal role during central nervous system development and the provision of docosahexaenoic acid (DHA) is recommended for the preterm infant. However, there are concerns that oral fish oil, which is a good source of DHA, may adversely affect growth of preterm infants, as it decreases arachidonic acid (ARA). It has been about ten years since fish oil was added to the fat blend of intravenous (IV) lipid emulsions (LE) but information on growth and other clinical outcomes of preterm infants is still scarce. We studied the effect of fish oil containing IV LE vs standard IV LE on growth in a large cohort of preterm infants who received routine parenteral nutrition (PN).

Methods: We retrospectively reviewed growth data of 546 preterm infants with a birth weight (BW) < 1250 g consecutively admitted to our NICU between Oct-2008 and Jun-2017 who received PN starting from the first day of life. Individual patients received only one of 5 commercially available IV LE. For the purpose of this study we grouped the patients who received the fish oil containing LE (**IV-FO**) and those who received conventional LE (**CNTR**). We compared PN and enteral nutrition (EN) intakes, and growth from birth to 36^{+0} weeks post-menstrual age (W PMA).

Results: Demographics, birth data and the incidence of the main complications of prematurity were similar between the two groups (IV-FO: n = 240, Gestational age (GA) 197 ± 16 d, BW 942 ± 181 g; CNTR: n = 237, GA 199 ± 17 d, BW 960 ± 197 g). No difference was found in PN and EN energy and macronutrient intakes from birth to 36^{+0}W PMA, as well as in the proportion of human milk to infant milk formula. Weight gain from the regained BW to 36^{+0}W PMA was slightly but significantly higher in IV-FO group: 17.3 ± 2.8 and 16.8 ± 2.7 $g \cdot kg^{-1} \cdot d^{-1}$, IV-FO and CNTR respectively (p = 0.03). There was no difference in length gain and head growth nor in body size at 36^{+0}W PMA between the two groups.

Conclusions: The use of IV fish oil did not negatively affect weight gain in a cohort of preterm infants. Large randomized controlled trials are needed to assess the effect of IV fish oil on the complication of prematurity and on selected domains of infant development.

1. Introduction

Long-chain polyunsaturated fatty acids (LCPUFA), in particular docosahexaenoic acid (DHA) and arachidonic acid (ARA), are in high proportions in structural lipids of cell membranes and play a major role during central nervous system development. Their accretion primarily occurs during the third trimester of gestation, thus infants born prematurely are deprived of the trans-placental passage of these essential lipids [1]. Human milk contains variable amounts of LCPUFA, depending on the mother's diet. Studies in

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Abbreviations

AA	amino acids
ARA	arachidonic acid
BW	birth weight
BPD	bronchopulmonary dysplasia
DHA	docosahexaenoic acid
ELBW	extremely low birth weight
EN	enteral nutrition
EOS	early onset sepsis
GA	gestational age
HC	head circumference
HM	human milk
IMF	infant milk formula
IQR	interquartile range
IV	intravenous
IVH	intraventricular hemorrhage
LE	lipid emulsion
L	length
LCPUFA	long chain polyunsaturated fatty acids
LOS	late onset sepsis
MCT	medium chain triglycerides
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
NPE	non protein energy
PDA	patent ductus arteriosus
PMA	post menstrual age
PN	parenteral nutrition
PVL	periventricular leukomalacia
RCT	randomized controlled trial
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
SDS	standard deviation score
W	week
WT	weight

preterm infants showed benefits of LCPUFA supplementation for retinal and cognitive development. Thus, the provision of DHA is now recommended for the preterm infant [2,3].

There is still a concern that oral fish oil, which is often used as a source of DHA, could impair growth of preterm infants, as some studies in the early '90s showed that enteral supplementation of marine oil was associated with poorer growth than in control infants [4–9]. The negative effect of oral fish oil on growth was attributed to the low plasma level of ARA of the marine oil supplemented infants [4]. In the subsequent 20 years no new data became available to confirm or refute these findings, as a source of ARA was added to the fat blend together with fish oil to ensure an adequate omega 6/omega 3 LCPUFA ratio [2].

It has been about ten years since fish oil was added to the fat blend of the intravenous (IV) lipid emulsions (LE) used for parenteral nutrition (PN). Information on the impact of fish oil containing LE on growth and other clinical outcomes in preterm infants is still scarce. Our group showed that a fish oil containing LE in extremely low birth weight (ELBW) preterm infants receiving routine PN was associated with a statistically significant reduction not only of ARA but also of free cholesterol, cholesterol esters and phospholipids [10]. In that study there was no difference in plasma triglycerides. In addition, a lipid lowering effect, mainly on plasma triglycerides, was reported in several adult studies where pharmaceutical doses of oral fish oil were given either for their lipid lowering effect and for the prevention of cardiovascular diseases [11]. We recently studied cholesterol biosynthesis and lipogenesis in preterm infants on PN, randomized to receive 10% fish oil or a standard LE and found a marginal but measurable reduction of lipogenesis in the IV fish oil group in comparison with a control group who received a LE of similar fatty acid composition but without fish oil [12]. In our view, if reducing plasma triglycerides/lipids in adults seems to be desirable, the same may not be true in the case of the small preterm infant. As plasma lipids probably reflect the trafficking/availability of the fatty acids, including essential LCPUFA, to the growing organs, the safety of any plasma lipid reducing intervention should be tested in follow up studies, including respiratory outcomes/bronchopulmonary dysplasia and brain growth/neurodevelopment.

A recent study, the N3RO trial, that aimed at giving to preterm infants enteral DHA at 60 mg/kg/day starting within 3 days of first enteral feed, showed an increased risk of bronchopulmonary dysplasia in the intervention group; this finding raised a renewed concern about the possible negative effect of marine oils in preterm infants [13].

To date, only few studies about the use of IV fish oil for the PN of the preterm infant reported growth data, mainly as secondary outcomes. A recent meta-analysis did not report significant differences in growth or in the main complications of prematurity between fish oil LE and controls, but evidence was too low grade to draw firm conclusions [14].

The aim of this study was to retrospectively review the growth of a rather large cohort of preterm infants on PN with different LE, with and without fish oil.

2. Materials and methods

2.1. Study design and participants

We retrospectively reviewed data on preterm infants admitted to the neonatal intensive care unit (NICU) of "G. Salesi" Children's Hospital, Ancona, Italy, between October 2008 and June 2017. Neonates with a birth weight (BW) of 400–1249 g and a gestational age (GA) at birth of at least 24^{+0} weeks (W) of postmenstrual age (PMA) and below 36^{+0} W PMA, in-born or out-born admitted before 24 h of age, who routinely received PN from the first day of life, were evaluated in this study. Individual patients received only one of the 5 LE used, sometimes as part of clinical trials (RCT) conducted during this ten year period in the NICU, with randomization according to the trial protocol presented previously [12,15,16]. Patients not enrolled in trials received nevertheless one of the 5 LE routinely acquired by the hospital pharmacy and assigned at birth by the neonatologist according to the pharmacy availability (more than one LE is always available at the hospital pharmacy). LE were: 1 = MSF (40:50 medium chain triglycerides-MCT: Soybean oil, 10% fish oil-FO; Lipidem®, B Braun), 2 = MOSF (30:30:25 MCT:Soybean oil:olive oil, 15% FO; SMOFlipid®, Fresenius Kabi), 3 = S (100% soybean oil; Intralipid®, Fresenius Kabi), 4 = MS (50%MCT and 50%Soybean oil; Lipofundin MCT®, B Braun) and 5 = OS (80% olive oil and 20% Soybean oil; Clinoleic®, Baxter spa). PN was an individualized all-in-one mixture for all the preterm infants evaluated in this study and the PN bags containing the study LE were of the same size and were of identical appearance. Caregivers involved with data collection were unaware of the LE assignment. To the purpose of this study we grouped the patients who received the fish oil containing LE MSF and MOSF (**IV-FO**) and those without fish oil S, MS and OS (**CNTR**).

Exclusion criteria were severe malformations, inborn errors of metabolism, death in the first day of life without receiving PN,

neonatal transfer in another NICU before 24 h of life and start of PN after 24 h of life. This retrospective study was approved by the local ethics committee (Prot. N. 2017 0503 OR; Det. N. 145/DG).

2.2. Nutrition protocol management

Patients started PN with glucose, amino acids, and lipids in the first day of life, according to the NICU Nutrition Schemes. The Nutrition Protocols of the different RCT since 2008 onward and Nutrition Schemes used in the NICU as guidelines for ELBW infants had similar daily progressive intakes. LE were infused at dose of 1–1.5 $g \cdot kg^{-1} \cdot d^{-1}$on the first day of life up to 2.5–3.5 $g \cdot kg^{-1} \cdot d^{-1}$ on the 5th day of life. Glucose was increased from 6–8 $g \cdot kg^{-1} \cdot d^{-1}$ to 12–14 $g \cdot kg^{-1} \cdot d^{-1}$ from day 1 to day 5. Amino acids were started at dose of 1–1.5 $g \cdot kg^{-1} \cdot d^{-1}$ in the first day of life and increased up to 2.5–3.5 $g \cdot kg^{-1} \cdot d^{-1}$on the 5th day of life. Maximum lipid, amino acid and glucose intakes achieved were then kept constant from day 5 to day 7. Minimal enteral feeding with human milk or infant milk formula was provided from day 0 to day 7, the maximum amount supplied being 8 $mL \cdot kg^{-1} \cdot d^{-1}$ from day 1 to day 4, and 16 $mL \cdot kg^{-1} \cdot d^{-1}$ from day 5 to day 7. For each infant after day 7, PN was tapered and stopped at a median age of 18 day of life while oral feeding was gradually increased to reach full feed and keep a maximum total fluid intake of 160 $mL \cdot kg^{-1} \cdot d^{-1}$.

2.3. Data collection and analysis

Detailed information on nutrition and growth was prospectively recorded daily with complete records of amount and type of enteral nutrition and PN, using a dedicated software (Neotools; Interactive, Milan, Italy). Body weight (WT) was measured daily using a digital infant scale; length (L) and head circumference (HC) were measured at birth and weekly thereafter using a neonatal stadiometer and a flexible non-stretchable tape respectively. Standard deviation scores (SDS) were computed using Italian growth charts. WT gain ($g \cdot kg^{-1} \cdot d^{-1}$) was calculated from birth to 36^{+0}W PMA and from the regained birth WT to 36^{+0}W PMA (mean of the day-by-day WT gain expressed in $g \cdot kg^{-1} \cdot d^{-1}$ of each study patient). Moreover, we used an additional method to calculate patient's growth. The WT gain ($g \cdot d^{-1}$) from the 10th day of life (that is the estimated mean time to the regained BW in our cohort) until 36^{+0}W PMA, the L gain (cm/w) and HC gain (cm/w) from birth and from the 5th day of life until 36^{+0}W PMA were calculated by using a simple linear regression fitting model. The major diagnosis/complications of prematurity were defined according to the Vermont–Oxford definitions, and the physiological definition of bronchopulmonary dysplasia was used according to Walsh et al. [17]. Cholestasis was defined as plasma direct bilirubin concentration above 1 mg/dl.

Sample size was calculated according to data available about WT gain from the regained BW to 36^{+0}W PMA in our cohort: patients admitted to our NICU who received PN with a conventional LE had a WT gain of 17.2 ± 3.02 $g \cdot kg^{-1} \cdot d^{-1}$. According to our database, about 550 ELBW patients were admitted to our unit in the last 10 years. Assuming a patient drop of about one third after checking for inclusion/exclusion criteria, and same variance in WT gain in both study patients and controls, we estimated a sample of 200 patients per group to detect a difference of at least 1 $g \cdot kg^{-1} \cdot d^{-1}$ with a 90% power at a significance level of 0.05.

Depending on the distribution, data were expressed as group means ± SD, as the median (interquartile range [IQR]) or as a number (percentage). The clinical characteristics of the two groups were compared using the Student's *t*-test, Mann–Whitney test or χ^2 test as appropriate. Significance was set at $p < 0.05$.

All statistical analyses were performed using SPSS (v 23.0; SPSS Inc, Chicago, Illinois) and Microsoft EXCEL (v 2016; Microsoft Corp, Redmond, Washington) software.

3. Results

From October 2008 to June 2017 all the records of 546 consecutively preterm infants admitted to the neonatal intensive care unit were screened for this study. Sixty-nine patients were excluded because they did not meet inclusion criteria: 18 patients because admitted after 24 h of life, 27 patients because of congenital malformations, 10 patients who died in the first day of life (without receiving PN), one patient transferred before 24 h of life because of shortage of beds and 13 patients in whom PN was started after 24 h of life. Four hundred seventy-seven preterm infants were studied of whom 240 received one of the two fish oil containing LE (**IV-FO group**) and 237 received one of the three conventional LE (**CNTR group**). Thirty-seven patients died before 36^{+0}W PMA (IV-FO n = 19, CNTR n = 18). Four hundred forty patients were finally analyzed for the assessment of growth, nutritional data and outcomes at 36^{+0}W PMA, 221 in the IV-FO group (MSF n = 131, MOSF n = 90) and 219 in the CNTR group (MS n = 163, OS n = 21, S n = 35).

Anthropometry at birth was similar between the two groups. A slight but significant difference in prenatal exposure to steroids was found, with a greater proportion of patients in the IV-FO group that received antenatal betamethasone (Table 1).

No significant differences were found in the incidence of the main complications of prematurity recorded from birth to 36^{+0}W PMA (Table 2).

We found no differences in parenteral and enteral nutritional intakes between the two study groups from birth to 36^{+0}W PMA. The proportion of human milk over the total enteral milk volume was also not different (Table 3).

The two groups were also similar in the incidence of surfactant therapy after birth (52% vs 54% in IV-FO and CNTR, p = 0.7), incidence of post-natal steroid treatment (11% vs 8%, IV-FO and CNTR, p = 0.3), number of days of respiratory support (32 d [5–59] vs 31 d [6–54] in IV-FO and CNTR, p = 0.7) or duration of oxygen therapy (363 h [3–1336] vs 301 h [9–1189] in IV-FO and CNTR, p = 0.8) from birth to 36^{+0}W PMA.

Table 1
Demographics and clinical characteristics at birth.

	IV-FO (n = 240)[a]	CNTR (n = 237)[b]	p
M/F– no. (%)	121/119 (50/50)	110/127 (46/54)	0.4
GA (w)	28 ± 2	28 ± 2	0.5
BW (g)	942 ± 181	960 ± 197	0.3
Z- score	−0.7 ± 1.0	−0.7 ± 1.1	0.8
Birth length (cm)	35.3 ± 2.8	35.5 ± 2.8	0.4
Z-score	−0.7 ± 1.0	−0.6 ± 1.0	0.7
Birth Head Circumference (cm)	25.2 ± 1.9	25.3 ± 1.9	0.6
Z-score	−0.5 ± 1.0	−0.4 ± 1.1	0.9
SGA 10p – no. (%)	93 (39)	91 (38)	0.9
SGA 2SDS – no. (%)	29 (12)	35 (15)	0.4
Exposure to antenatal glucocorticoids-no. (%)	227 (95)	212 (90)	0.04
APGAR at 5 min- median (IQR)	8 (7–9)	8 (7–9)	0.5

Data are expressed as Mean ± SD, unless otherwise indicated, $p < 0.05$ (Student's t-test, Mann–Whitney test or χ^2 test, as appropriate).
GA: gestational age; BW: birth weight; SDS: standard deviation score; SGA: small for gestational age.
[a] MSF (Lipidem®; B Braun): 50% medium chain triglycerides (MCT), 40% soybean oil (SO), and 10% fish oil; MOSF (SMOFlipid®; Fresenius Kabi): 30:30:25 MCT:Soybean oil:olive oil, 15% FO.
[b] MS (Lipofundin MCT®; B Braun): 50% MCT and 50% SO; S (Intralipid®; Fresenius Kabi): 100% soybean oil; OS (Clinoleic®; Baxter spa): 80% olive oil and 20% Soybean oil.

Table 2
Neonatal outcomes until 36^{+0} weeks postmenstrual age.

	IV-FO (n = 221)[a]	CNTR (n = 219)[b]	p
RDS (%)	174 (79)	185 (85)	0.1
PDA (%)	131 (59)	127 (58)	0.8
NEC ≥ 2 (%)	9 (4)	10 (5)	0.8
IVH ≥ 3 (%)	14 (6)	21 (10)	0.2
Cystic PVL (%)	6 (3)	4 (2)	0.5
ROP ≥ 3 (%)	0 (0)	1 (1)	0.5
BPD (%)	59 (27)	45 (21)	0.1
EOS (%)	8 (4)	7 (3)	0.8
LOS (%)	43 (20)	36 (16)	0.4
Cholestasis (%)	31 (14)	31 (14)	1.0

Data are expressed as no (%), $p < 0.05$ (χ^2 test).
RDS: respiratory distress syndrome; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity; BPD: bronchopulmonary dysplasia; EOS: early onset sepsis; LOS: late onset sepsis.
[a] MSF (Lipidem®; B Braun): 50% medium chain triglycerides (MCT), 40% soybean oil (SO), and 10% fish oil; MOSF (SMOFlipid®; Fresenius Kabi): 30:30:25 MCT:Soybean oil:olive oil, 15% FO.
[b] MS (Lipofundin MCT®; B Braun): 50% MCT and 50% SO; S (Intralipid®; Fresenius Kabi): 100% soybean oil; OS (Clinoleic®; Baxter spa): 80% olive oil and 20% Soybean oil.

Table 3
Cumulative and mean daily nutritional intakes until 36^{+0} weeks postmenstrual age.

	IV-FO (n = 221)[a]	CNTR (n = 219)[b]	p
PN^{Cum} AA (g/kg)	37 (32–49)	37 (32–48)	0.8
PN^{Cum} NPE (Kcal/kg)	768 (671–1020)	768 (669–980)	0.8
EN^{Cum} Protein (g/kg)	149 (97–190)	148 (100–188)	0.9
EN^{Cum} NPE (Kcal/kg)	4435 (3129–5567)	4354 (3189–5571)	0.8
$Fluids^{Cum}$ (ml/kg)	8611 (6514–9968)	8195 (6267–9905)	0.4
HM^{Cum} (ml/kg)	4377 (1946–6235)	4132 (2071–6280)	0.8
IMF^{Cum} (ml/kg)	1442 (238–3858)	1407 (141–4387)	0.9
PN AA (g/kg/d)	2.1 ± 0.4	2.1 ± 0.3	0.4
PN NPE (Kcal/kg/d)	45 ± 5.6	45 ± 5.5	0.8
EN Protein (g/kg/d)	2.8 ± 0.7	2.8 ± 0.6	0.8
EN NPE (Kcal/kg/d)	83 ± 17	83 ± 15	0.9
Fluids (ml/kg/d)	154 ± 8	154 ± 9	0.2

Data are expressed as Median (IQR) or mean (SD), $p < 0.05$ (Mann–Whitney or Student t-test as appropriate).
PN^{Cum}: parenteral nutrition cumulative intakes from birth to 36^{+0}W PMA; EN^{Cum}: enteral nutrition cumulative intakes from birth to 36^{+0}W PMA; AA: amino acids; NPE: non-protein energy; HM: human milk; IMF: infant milk formula.
[a] MSF (Lipidem®; B Braun): 50% medium chain triglycerides (MCT), 40% soybean oil (SO), and 10% fish oil; MOSF (SMOFlipid®; Fresenius Kabi): 30:30:25 MCT:Soybean oil:olive oil, 15% FO.
[b] MS (Lipofundin MCT®; B Braun): 50% MCT and 50% SO; S (Intralipid®; Fresenius Kabi): 100% soybean oil; OS (Clinoleic®; Baxter spa): 80% olive oil and 20% Soybean oil.

There were no differences in WT loss, postnatal age at WT nadir, time to regain BW and weight gain during the first four weeks of life. Anthropometry at 36^{+0}W PMA was not significantly different between the two study groups (Table 4). We found a statistically higher WT gain from birth to 36^{+0}W PMA and from the regained BW to 36^{+0}W PMA and a significant higher WT-SDS gain from birth to 36^{+0}W PMA in the IV-FO group (Table 4). No differences were found in the absolute difference of gains of the other main anthropometric data. Growth calculated by a linear fitting model was not different between the two study groups: WT gain (10 days of life to 36^{+0}W PMA): 23.3 ± 5.8 vs 22.4 ± 5.2 $g \cdot d^{-1}$ ($p = 0.1$); L gain (birth to 36^{+0}W PMA): 1.1 ± 0.4 vs 1.1 ± 0.4 c/week ($p = 0.7$); HC gain (5 days of life to 36^{+0}W PMA): 0.9 ± 0.2 vs 0.8 ± 0.2 ($p = 0.2$), IV-FO group and CNTR respectively.

Table 4
Anthropometry and growth until 36^{+0} weeks postmenstrual age.

	IV-FO (n = 221)[a]	CNTR (n = 219)[b]	p
WT nadir (g)	827 ± 173	839 ± 181	0.5
Age at nadir (d)	4.4 ± 2.1	4.1 ± 1.6	0.1
WT loss at nadir (%)	12.3 ± 5.4	12.6 ± 5.5	0.6
Time to regain BW (d)	11.8 ± 5.1	11.9 ± 5.0	0.9
WT gain (1W) ($g \cdot kg^{-1} \cdot d^{-1}$)	−17.4 ± 13.5	−19.1 ± 13.8	0.2
WT gain (2W) ($g \cdot kg^{-1} \cdot d^{-1}$)	16.1 ± 10.2	16.6 ± 9.5	0.5
WT gain (3W) ($g \cdot kg^{-1} \cdot d^{-1}$)	15.2 ± 9.3	15.3 ± 8.7	0.9
WT gain (4W) ($g \cdot kg^{-1} \cdot d^{-1}$)	17.1 ± 8.3	16.6 ± 8.5	0.5
WT at 36^{+0}W PMA (g)	1912 ± 367	1870 ± 351	0.2
Z- score	−1.8 ± 0.9	−1.9 ± 0.9	0.2
L at 36^{+0}W PMA (cm)	42.5 ± 2.6	42.7 ± 2.4	0.4
Z-score	−1.9 ± 1.0	−1.8 ± 0.9	0.3
HC at 36^{+0}W PMA (cm)	30.6 ± 1.5	30.4 ± 1.5	0.4
Z-score	−1.6 ± 1.1	−1.6 ± 1.0	0.5
WT gain (Birth-36^{+0}W PMA) ($g \cdot kg^{-1} \cdot d^{-1}$)	16.0 ± 2.7	15.5 ± 2.7	0.03
WT gain (BW recovery-36^{+0}W PMA) ($g \cdot kg^{-1} \cdot d^{-1}$)	17.3 ± 2.8	16.8 ± 2.7	0.03
Δ WT (Birth-36^{+0}WPMA)	970 ± 353	910 ± 341	0.07
Δ L (Birth-36^{+0}WPMA)	7.2 ± 2.9	7.2 ± 2.9	0.9
Δ HC (Birth-36^{+0}WPMA)	5.3 ± 2.0	5.2 ± 2.0	0.3
Δ WT SDS (Birth-36^{+0}WPMA)	−1.0 ± 0.6	−1.2 ± 0.6	0.02
Δ L SDS (Birth-36^{+0}WPMA)	−1.3 ± 0.8	−1.2 ± 0.8	0.4
Δ HC SDS (Birth-36^{+0}WPMA)	−1.1 ± 1.0	−1.2 ± 1.0	0.5

Data are expressed as Mean ± SD, $p < 0.05$ (Student's t-test).
WT: weight; L: length; HC: head circumference; W: week; Δ WT (Birth-36^{+0}WPMA): difference in weight between birth and 36 weeks postmenstrual age (g); Δ L (Birth-36^{+0}WPMA): difference in length between birth and 36 weeks postmenstrual age (cm); Δ HC (Birth-36^{+0}WPMA): difference in head circumference between birth and 36 weeks postmenstrual age (cm); Δ WT SDS (Birth-36WPMA): difference in SDS of weight between birth and 36 weeks postmenstrual age; Δ L SDS (Birth-36WPMA): difference in SDS of length between birth and 36 weeks postmenstrual age; Δ HC SDS (Birth-36WPMA): difference in SDS of head circumference between birth and 36 weeks postmenstrual age.
[a] MSF (Lipidem®; B Braun): 50% medium chain triglycerides (MCT), 40% soybean oil (SO), and 10% fish oil; MOSF (SMOFlipid®; Fresenius Kabi): 30:30:25 MCT:Soybean oil:olive oil, 15% FO.
[b] MS (Lipofundin MCT®; B Braun): 50% MCT and 50% SO; S (Intralipid®; Fresenius Kabi): 100% soybean oil; OS (Clinoleic®; Baxter spa): 80% olive oil and 20% Soybean oil.

4. Discussion

To our knowledge this is the first report on growth in a rather large cohort of preterm infants who received routine PN from the first day of life. We found that the use of LE containing 10–15% of fish oil as part of the routine PN of ELBW infants during the first 3 weeks of life was associated with a slightly but significantly higher WT gain until 36^{+0}W PMA than controls. There was no difference in body size at 36^{+0}W PMA. In addition we found no difference in the main complications of prematurity.

To date, data about IV fish oil and growth of preterm infants are scanty and not conclusive. Six randomized controlled trials compared MOSF (containing 15% fish oil) versus a conventional 100% SO based LE (S) [15,16,18–21]. Two study reported data comparing a 10% fish oil LE (MSF) with SO LE [10,16] and one study compared MOSF patients versus an olive oil containing LE (OS) group [22]. Growth was a secondary outcome in all these studies, and none of them was powered to detect differences in growth.

MOSF and S were compared in three studies with no differences in growth, neither at the end of PN nor at hospital discharge. Of note, in two of these studies lipids were started at a variable length after birth (from the first four to seven days of life), the lipid infusion time ranged from 18 to 20 h per day and the target dose was reached after several days from the PN start [18,20]. The study by Skouroliakou compared 14 study infants versus 18 controls and was

clearly underpowered to detect growth differences [19]. D'Ascenzo et al. found a significantly greater postnatal WT loss and longer time to regain BW with MOSF LE in comparison with S (14.3 ± 5.8% vs 11.1 ± 5.7% and 13.4 ± 5.6 d vs 10.5 ± 5.1 d, MOSF and S groups respectively). WT gain until 36^{+0} W PMA was similar between the two groups (17.1 $g \cdot kg^{-1} \cdot d^{-1}$ vs 16.6 $g \cdot kg^{-1} \cdot d^{-1}$, MOSF and S groups respectively) [15]. Savini et al. described weekly growth rates in 174 infants with clinical characteristics similar to the present study and found no differences between MOSF and S, MSF and S and MSF and MS [16]. WT gain was 3.1 $g \cdot d^{-1}$ higher and HC z-score gain was 0.6 greater (both statistically significant) in 48 patients who received MOSF in comparison with 48 controls who received S LE in the study by Vlaardingerbroek et al. [21].

There is only one study comparing MSF and MS; in this study the author states that no differences in growth were found, but no data were provided [10]. Najm et al., in 2017 compared MOSF versus an olive oil containing LE (OS) in ELBW infants. IV lipids were started from the first day of life with daily increments up to 2 $g \cdot kg^{-1} \cdot d^{-1}$. Growth was not different between the study arms [22].

In the present study we report data from a rather homogenous population of preterm infants with a BW of less than 1250 g who all received routine PN starting in the first day of life. Demographics and clinical characteristics at birth were rather similar between the two groups, except for a statistically higher proportion of antenatal steroids treatment in the IV-FO group. We interpret this as a chance finding due to multiple comparisons. In addition, albeit statistically significant, the difference in our opinion is likely to be biologically negligible. Early postnatal growth parameters (first four weeks of life, Table 4) were not different between the two groups. However, WT gain until 36^{+0}W PMA was significantly higher in the IV-FO group. Because of the study design, we are unable to answer the question if this difference should be attributed to PN, to enteral nutrition or both. The nutrient intake data reported in Table 3 clearly show that macronutrient and energy supplies were not different between the two groups, neither during PN nor during enteral nutrition. The two study groups did not differ also for the proportion of human milk to infant milk formula received. We are therefore unable to provide a solid interpretation for the statistically higher WT gain in the study group. In our view the higher WT gain in the IV-FO group although statistically significant, is biologically negligible; this view is also supported by the fact that we found no difference in length gain and in head growth. Moreover, complications of prematurity were not different in the two groups. These findings all together are in our view somewhat reassuring, as we feared (see introduction section) a potential negative effect of fish oil on the growth of preterm infants.

Even if this was not a randomized controlled trial, the large cohort of preterm infants we analyzed, the standardized nutritional protocols used during the period in our NICU, and the homogeneity of the preterm population admitted, confer some degree of strength to our results and we believe selection bias if any was negligible. Moreover, growth data are slightly in favor of the IV-FO group, so that we can reasonably say that the use of 10–15% fish oil containing LE does not negatively affect short-term growth of ELBW preterm infants on PN.

In a study by Groh-Wargo et al., preterm infants fed a DHA and ARA supplemented formula from the first enteral feed to 12 months corrected age had greater lean body mass and reduced fat mass, with no differences in overall WT in comparison to controls [23]. This finding suggests a possible effect of LCPUFA supplementation on body composition, because of the net effect on hepatic and muscular cells metabolism. We therefore cannot exclude that even if anthropometry and growth were similar in patients who received IV fish oil and in controls, body composition could have been different.

In conclusion, this large retrospective study showed that administration of IV fish oil did not negatively affect short-term growth in preterm infants on PN, and add data about safety of its use in preterm infants. However, data are still of low grade evidence and no information is available about IV fish oil effects on the growth and development of selected organs, on body composition and on neurodevelopmental outcome. Further larger RCT are warranted to clarify these important clues of preterm infant care.

Statement of authorship

Contribution of each author:

- VPC was responsible for the design of the study;
- CB, RD, and MPB contributed to data collection and analysis;
- AC and AP contributed to subject recruitment and data collection;
- PEC, PM and LA were in charge of the statistical analysis.

All authors read and approved the final manuscript.

Conflict of interest statement and funding sources

There are no conflicts of interest to declare.

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