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What is the relationship between gestational age and docosahexaenoic acid (DHA) and arachidonic acid (ARA) levels?

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ABSTRACT

Long chain polyunsaturated fatty acids (LCPUFA) including docosahexaenoic acid (DHA) and arachidonic acid (ARA) are increasingly transferred from mother to fetus late in pregnancy. Infants born before this transfer is complete are at risk for deficiency. This study determines the relationship between gestational age (GA) and circulating LCPUFA levels to better understand the unique needs of premature infants born at various GAs. Whole blood was collected within the first 7 days of life from 60 preterm (≤ 34 weeks GA) and 30 term infants (≥ 38 weeks GA) and FA levels were analyzed. Since concurrent intravenous lipid emulsion can skew composition data, blood LCPUFA concentrations were also measured. Levels were compared among groups, and linear regression models were used to examine the association between FA composition and GA. Preterm infants had significantly lower DHA and ARA levels than term peers, and whether assessed as concentrations or compositions, both directly correlated with GA ($p < 0.0001$). Moreover, FA comparisons suggest that premature infants have impaired synthesis of LCPUFAs from precursors and may require preformed DHA and ARA. This study confirms that essential FA status is strongly related to GA, and that those babies born the earliest are at the greatest risk of LCPUFA deficiency.

1. Introduction

Premature birth is a leading cause of infant morbidity and mortality, and as survival has increased, there is renewed focus on improving both short- and long-term outcomes in this high-risk population. One way to do this is through tailored provision of key nutrients. Long chain polyunsaturated FAs (LCPUFAs), including arachidonic acid (ARA) and docosahexaenoic acid (DHA), are important for normal health and development [1,2]. Increasing evidence demonstrates that DHA supplementation improves visual outcomes [3–5] and neurodevelopment [6–9] in premature infants and may decrease morbidity from bronchopulmonary dysplasia [10], necrotizing enterocolitis [11–14] and retinopathy of prematurity [15–17]. Although supplementation studies are promising, the optimal amount of individual fatty acids (FAs) needed at various gestational ages (GA) is still relatively unknown [1].

There are two important families of essential LCPUFAs, the omega-6 FAs including ARA (20:4n-6) and its 18-carbon precursor linoleic acid (LA, 18:2n-6), and the omega-3 FAs including eicosapentaenoic acid (EPA, 20:5n-3), DHA (22:6n-3) and their 18-carbon precursor α-linolenic acid (ALA, 18:3n-3). These two families have different functions and are not interchangeable, making provision of both essential. The developing fetus is dependent on a maternal source during pregnancy. Most LCPUFA accumulation occurs during the third trimester [18,19] and so, infants born before this process is complete are at risk of deficiency.

Previous studies have analyzed LCPUFA status in premature babies, most commonly as part of an intervention study [10,20–27]. However, to our knowledge, only two studies have directly compared blood FAs between term and preterm infants across a range of GAs [10,20]. Both studies analyzed a composition or weight percent of total blood FAs that could be influenced by the simultaneous infusion of lipid emulsions commonly administered within the first week of life to pre-term infants. This leaves some question regarding the exact relationship between LCPUFA status and GA. As part of a randomized trial of the use of enteral DHA

Abbreviations: LCPUFA, long chain polyunsaturated fatty acids; GA, gestational age; FA, fatty acid; DHA, docosahexaenoic acid; ARA, arachidonic acid; LA, linoleic acid; ALA, α-linolenic acid; SGA, small for gestational age; WHO, World Health Organization; FGC, Fenton Growth Curve; NICU, neonatal intensive care unit.

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supplementation in premature infants, we measured baseline blood FAs as both a percent composition and actual concentration and investigated the relationship of LCPUFAs with GA.

2. Patients and methods

2.1. Study population

Ninety infants (60 preterm and 30 term infants) who met study criteria were recruited from the Boekelheide NICU at Sanford Children's Hospital between October 2012 and March 2014. Eligible preterm infants were less than or equal to seven days of age at enrollment and were further stratified into two groups: early preterm (GA of 24 0/7 to 27 6/7 weeks at birth) and late preterm (GA 28 0/7 to 34 0/7 weeks at birth). Preterm infants were excluded if they were considered non-viable by the medical team, or if they had multiple, severe congenital anomalies. Term infants (38 weeks GA or greater at birth) were excluded if they were born to diabetic mothers or were small for GA (SGA) which was defined by a birth weight less than the 10th% for adjusted GA on a World Health Organization (WHO) growth chart. These exclusion criteria for reference term infants were used because of previously reported differences in FA accretion in these groups [20,28–31]. Infants were prospectively enrolled using an adaptive enrollment method to assure that early preterm infants were included in the study during the same time period as more commonly admitted late preterm and term infants. The study was approved by the Sanford Institutional Review Board, and all mothers (who had to be at least 18 years of age) provided written, informed consent after all procedures had been thoroughly explained and prior to their infant's participation.

2.2. Clinical data

Clinical data for enrolled infants and their mothers were collected from electronic medical records following HIPPA authorization. Maternal data included age, gravidity, parity, race, and obstetric estimate of GA at delivery. Maternal diabetes status was determined by the medical problem list and results of an oral glucose tolerance test if completed during the pregnancy. Baseline infant data included estimated GA at birth, sex, mode of delivery, reported race, day of life, birth weight, height, head circumference and growth chart percentile (Fenton Growth Curve, FGC, for preterm infants and WHO Growth Chart for term infants).

Per the standard of care in our NICU, premature infants begin receiving total parenteral nutrition on the first day of life which includes 10% soybean oil-based intravenous lipid emulsion (Intralipid®) titrated to a typical dose of 2–3 g/kg/d by the third day of life. Parenteral lipid emulsion is typically continued until they reach "full enteral feedings" (100 kcal/kg/day of breast milk or formula). In our study population, late preterm infants reached "full enteral feedings" at a mean (SD) of 15.1 (5.1) days, and early preterm infants at 29.5 (7.2) days. Thus, at the time of baseline analysis (average 6.3 days of life), all premature infants were receiving a significant amount of LA and ALA, but no ARA and DHA, from parenteral lipid administration. Emulsions containing fish oil (Omegaven®) were not used in this study.

2.3. Dried blood spot (DBS) fatty acid analysis

Following enrollment, a single drop of scavenged whole blood was collected directly to a filter paper (Ahlstrom 226, PerkinElmer, Greenville, SC) that was pretreated with an antioxidant cocktail (Oxystop, OmegaQuant Analytics, LLC, Sioux Falls, SD) to protect unsaturated FAs from oxidation. Whole blood was chosen as the sample of choice because it is a global representation of circulating FA status (including both plasma and blood cells) and because analyses can be conducted on as little as a single drop. After collection, cards were stored in a re-sealable plastic bag at 4 °C with batches delivered weekly to OmegaQuant Analytics for analysis by capillary gas chromatography as described previously [32]. Fatty acid levels are expressed both as a weight percent of total blood fatty acids (composition) and as a concentration (μg/mL blood). The latter was calculated based on the internal standard (22:3n-3) included in the assay and on the experimental determination that the average volume of dried blood contained in a 4-mm punch was 9.7 μL. The mean time between sample collection and analysis in this study was 6.8 days. The stability of FAs collected and stored in this manner has been previously evaluated by analyzing 5 blood samples (not from this study) weekly over a 4 week time period. There was no sample degradation detected [33]. Specifically, mean baseline and 4 week values were: ARA, 11.3% and 12.0%; and DHA, 4.5% and 4.3%. Coefficients of variation were 2.5% and 5.8%, respectively.

2.4. Statistical analysis

For continuous variables, means and standard deviations were calculated. Categorical variables were described using frequencies and percents. Univariate analysis of all FAs was performed using the Kruskal–Wallis test. Linear mixed models were used to examine the association between FA composition and GA. The mixed model accounts for possible correlation between twins and triplets present in the data set. The model covariance was assessed to determine if a mixed model was needed or if the assumption of independence could be made. For all models, the assumption of independence was justified, so linear regression models without a random effect were used. Continuous dependent variables were transformed as needed to meet model assumptions. Models were adjusted for maternal age, timing of blood collection and relative weight, and head circumference (growth curve percentiles) at birth. Primary outcome variables for this analysis were DHA and ARA as both compositions and concentrations. Model diagnostics were examined to ensure that models were not overly influenced by outliers. Additionally, two-sensitivity analyses were undertaken to examine the effect of inclusion criteria (preterm infants who were SGA or whose mother had diabetes during the pregnancy) and the day of sample collection. Results for both sensitivity analyses produced largely similar parameter estimates and therefore are not reported separately.

3. Results

3.1. Study population

A total of 140 preterm and 176 term infants were screened and found to be eligible for the study. Thirty term infants and 60 preterm infants were enrolled. Of the latter, 47 were late preterm and 13 were early preterm (Table 1). For the preterm infants, the most common reason for not enrolling was parental refusal to participate in the DHA intervention study. For the term infants, the most common reasons were that the infant's heel sticks were already done or that the target enrollment for term infants had already been met for that period (i.e., as noted above, the rate of preterm infant enrollment determined the rate of term infant enrollment using our adaptive enrollment method to ensure enrollment of infants from each GA over a similar time period).

3.2. Blood fatty acid status

The average day of life at baseline collection was 6.3 days for the preterm infants and 2.9 days for term infants. Of the 30 term and 60

Table 1
Infant characteristics.

Variable	Category	Early preterm $N=13$	Late preterm $N=47$	Term $N=30$
Gender *N* (%)	Male	8 (61.5)	22 (46.8)	18 (60.0)
	Female	5 (38.5)	25 (53.2)	12 (40.0)
Ethnicity *N* (%)	Non-Hispanic	12 (92.3)	42 (89.4)	28 (93.3)
	Unavailable/unknown	1 (7.7)	4 (8.5)	2 (6.7)
	Declined	0 (0.0)	1 (2.1)	0 (0.0)
Race *N* (%)	Caucasian/White	10 (76.9)	43 (91.5)	28 (93.3)
	Unavailable/unknown	1 (7.7)	0 (0.0)	0 (0.0)
	Native American	2 (15.4)	3 (6.4)	2 (6.7)
	Native Hawaiian/Pacific Islander	0 (0.0)	1 (2.1)	0 (0.0)
Diabetic mother *N* (%)	Yes	2 (15.4)	3 (6.4)	0 (0.0)
	No	11 (84.6)	44 (93.6)	30 (100.0)
Type of birth *N* (%)	Singleton	11 (84.6)	23 (48.9)	30 (100.0)
	Twins	2 (15.4)	18 (38.3)	0 (0.0)
	Triplets	0 (0.0)	6 (12.8)	0 (0.0)
Birth length (%) mean (SD)		34.25[a] (26.43)	35.83[a] (26.89)	60.87[b] (22.68)
Birth weight (%) mean (SD)		55.31[a] (26.70)	42.60[a] (22.11)	52.03[b] (16.66)
Maternal age mean years (SD)		27.00 (4.93)	30.60 (5.51)	26.79 (5.56)
GA range		25–28	29–33	38–40

[a] Percentile on Fenton Growth Curve for premature infants.
[b] Percentile on WHO Growth Chart for term infants.

preterm infants enrolled, one preterm blood sample was damaged and could not be used, and one term infant was enrolled but discharged prior to sample collection. This left 29 term and 59 preterm participants with useable whole blood FA analyses.

When early and late preterm infants were compared with term infants, ARA levels were 27% and 12% lower when expressed as composition (percent of whole blood FAs) and were 27% and 15% lower when expressed as concentrations, respectively (Table 2). A similar pattern was found for DHA, where levels were 46% and 29% lower when expressed as a percent, and were 48% and 31% lower when expressed as concentrations. Therefore, whether expressed as composition or concentration, the gradients in FA levels were similar across the GA spectrum, with levels of both ARA and DHA being the lowest in the early preterms, intermediate in the late preterms and highest in the term infants. Interestingly, despite the infusion of intravenous lipid emulsion, circulating total FA concentrations did not vary across the GA spectrum. For the early-preterm, late-preterm and term infants the mean (SD) FA concentrations in μg/mL were 994 (420), 931 (222) and 952 (241), respectively. This may be why compositions and concentrations of individual FAs were similar.

These univariate trends between GA and ARA and DHA were also seen in the multivariable models using a natural logarithm transformation which included adjustments for maternal age, day of blood collection, and growth percentiles for weight and head circumference (Table 3). Indeed, DHA levels were 4.3% or 3.7% higher (composition or concentration) and ARA levels were 2.2% or 1.6% higher (composition or concentration) for each additional week of GA gained prior to birth. These relationships are illustrated in Figs. 1 and 2.

Blood levels of the precursor essential FAs, LA (C18:2n6) and ALA (C18:3n3), varied markedly by GA (Table 2). Levels were much higher in early and late preterm infants compared with the term infants. LA concentrations were 188% and 95% higher, and ALA concentrations 894% and 334% higher, respectively. Similar patterns were also seen in percent composition. The elongation product of LA (C20:2n6) was elevated in the preterm infants compared with the term infants, but all of its desaturation/elongation metabolites (C20:3n6, ARA, C22:4n6, and C22:5n6) were depressed. This was observed for both percent composition and concentration.

4. Discussion and conclusions

4.1. Discussion

In this cross sectional study comparing blood FA levels we observed lower ARA and DHA levels in preterm compared to term infants and demonstrated a direct correlation between these essential LCPUFAs and GA; thus very preterm infants have the highest risk of deficiency. Importantly, this was true whether expressed as a percent of total blood FAs (composition) or concentration which were feasibly measured using a dried blood spot methodology. Comparison of all FAs suggests that premature infants have impaired biosynthesis of LCPUFAs from precursor FAs compared to term infants and may require preformed provision of ARA and DHA.

Two previous studies have directly compared preterm to term LCPUFA status. First Agostoni et al. reported reduced DHA, but not ARA, composition in late preterm (average of 35 weeks GA) vs. term (average of 38 weeks GA) infants who were studied at day 4 of life [20]. Infants who required intravenous lipid infusions (which could artificially alter FA status when reported as a percent of total blood FAs) were excluded from this study. DHA levels were 2.8% in preterm (mean 35 weeks GA) and 3.9% in term infants (mean 38 weeks GA; $p < 0.05$) [20]. Our findings, particularly those based on LCPUFA concentrations (which would be insensitive to dilution by intravenous lipids), support these findings from Italy. By design, Agostoni's study [20] was limited to relatively healthy, older GA participants who did not require intravenous lipid emulsion and so conclusions about very premature infants could not be drawn.

Martin et al. included infants born at earlier GAs and found no difference in either ARA or DHA composition between premature (mean 27 weeks) and term (> 37 weeks) infants at birth [10]. However, by one week of age, DHA *composition* decreased 40% from 6.9% to 4.2% at the same time that LA levels increased from 7% to 19% of total FAs [10]. Because commercially available lipid emulsions contain precursor LA (50% of soy based emulsion) and ALA (9%) but do not contain preformed ARA or DHA, Martin's findings could simply reflect a dilution of circulating DHA from other intravenously infused lipids or a decreased in vivo synthesis due to competition from ARA precursors (LA) through the same biosynthetic pathway.

Table 2
Blood fatty acid levels (percent composition and concentration in early and late pre-term and term infants.

Fatty acids expressed as percent of total blood fatty acids					Percent differences vs term		**Fatty acids expressed as a concentration in whole blood (μg/mL)**				Percent differences vs term	
Fatty acid	Early pre-term ($n=13$)	Late pre-term ($n=46$)	Term ($n=29$)	***p*-Value**	Early (%)	Late (%)	Early Pre-term ($n=13$)	Late pre-term ($n=46$)	Term ($n=29$)	***p*-Value**	Early (%)	Late (%)
C22:6n3 (DHA)	2.66% (0.64)	3.53% (0.54)	4.97% (1.08)	< 0.0001	−46	−29	24.99 (5.87)	32.73 (7.41)	47.66 (15.97)	< 0.001	−48	−31
C20:4n6 (ARA)	12.19% (2.21)	14.52% (1.97)	16.59% (1.69)	< 0.0001	−27	−12	115.73 (25.43)	134.41 (28.26)	158.75 (37.87)	< 0.001	−27	−15
Other fatty acids												
C14:0	0.39% (0.15)	0.56% (0.45)	0.66% (0.19)	< 0.0001	−41	−15	3.76 (1.5)	5.42 (5.84)	6.28 (2.22)	< 0.001	−40	−14
C16:0	22.2% (1.70)	23.78% (0.97)	26.2% (1.44)	< 0.0001	−15	−9	216.95 (68.52)	221.11 (42.80)	249.23 (53.08)	0.003	−13	−11
C16:1n7t	0.07% (0.05)	0.07% (0.04)	0.08% (0.05)	0.69	−13	−13	0.61 (0.29)	0.68 (0.43)	0.76 (0.39)	0.46	−20	−11
C16:1n7	0.43% (0.33)	0.51% (0.16)	1.25% (0.46)	< 0.0001	−66	−59	4.13 (2.76)	4.77 (2.02)	11.81 (4.75)	< 0.001	−65	−60
C18:0	13.28% (1.70)	14.44% (1.18)	15.1% (0.69)	0.0006	−12	−4	127.96 (32.458)	133.92 (26.12)	143.95 (30.75)	0.05	−11	−7
C18:1t	0.25% (0.05)	0.36% (0.18)	0.33% (0.13)	0.04	−24	9	2.52 (1.06)	3.42 (1.88)	3.13 (1.28)	0.2	−19	9
C18:1n9	17.88% (1.80)	16.16% (1.29)	15.83% (1.36)	0.002	13	2	182.04 (88.98)	151.06 (34.5)	150.69 (33.03)	0.42	21	0
C18:2n6t	0.35% (0.09)	0.36% (0.10)	0.38% (0.12)	0.56	−8	−5	3.32 (1.09)	3.37 (1.14)	3.59 (1.97)	0.56	−8	−6
C18:2n6	21.66% (5.16)	16.6% (3.08)	8.42% (2.72)	< 0.0001	157	97	229.37 (159.41)	155.65 (45.22)	79.67 (30.2)	< 0.001	188	95
C20:0	0.28% (0.05)	0.28% (0.04)	0.25% (0.05)	0.0004	12	12	2.68 (0.67)	2.55 (0.47)	2.29 (0.41)	0.03	17	11
C18:3n6	0.16% (0.07)	0.13% (0.04)	0.08% (0.03)	< 0.0001	100	63	1.61 (0.79)	1.25 (0.48)	0.8 (0.29)	< 0.001	101	56
C20:1n9	0.21% (0.03)	0.22% (0.06)	0.2% (0.07)	0.12	5	10	2.07 (0.84)	2.06 (0.60)	1.89 (0.71)	0.4	10	9
C18:3n3	1.07% (0.49)	0.53% (0.33)	0.13% (0.08)	< 0.0001	723	308	11.53 (9.63)	5.04 (3.67)	1.16 (0.80)	< 0.001	894	334
C20:2n6	0.39% (0.08)	0.39% (0.11)	0.23% (0.07)	< 0.0001	70	70	3.76 (1.11)	3.65 (1.12)	2.13 (0.68)	< 0.001	77	71
C22:0	0.54% (0.10)	0.51% (0.12)	0.46% (0.13)	0.02	17	11	5.11 (1.05)	4.68 (0.93)	4.18 (0.85)	0.009	22	12
C20:3n6	1.75% (0.56)	2.1% (0.44)	2.48% (0.46)	< 0.0001	−29	−15	16.57 (5.83)	19.43 (5.27)	23.54 (6.30)	< 0.001	−30	−17
C24:0	0.37% (0.10)	0.36% (0.09)	0.37% (0.07)	0.54	0	−3	3.44 (0.69)	3.32 (0.89)	3.46 (0.74)	0.54	−1	−4
C20:5n3	0.35% (0.35)	0.33% (0.35)	0.35% (0.50)	0.45	0	−6	3.1 (3.04)	2.99 (3.21)	3.23 (4.63)	0.33	−4	−7
C24:1n9	0.28% (0.13)	0.27% (0.08)	0.24% (0.08)	0.19	17	13	2.57 (.82)	2.52 (0.79)	2.27 (0.67)	0.4	13	11
C22:4n6	2.01% (0.42)	2.54% (0.47)	3.46% (0.52)	< 0.0001	−42	−27	18.88 (4.11)	23.33 (4.85)	33.06 (8.34)	< 0.001	−43	−29
C22:5n6	0.73% (.20)	0.96% (0.26)	1.41% (0.33)	< 0.0001	−48	−32	6.95 (2.26)	8.82 (2.50)	13.44 (3.92)	< 0.001	−48	−34
C22:5n3	0.5% (0.21)	0.47% (0.13)	0.51% (0.11)	0.25	−2	−8	4.68 (1.77)	4.36 (1.51)	4.89 (1.57)	0.33	−4	−11

Table 3
*Regression model estimates for DHA and ARA concentration and percent composition.

	DHA blood concentration (μg/mL)			**ARA blood concentration (μg/mL)**		
Parameter	Estimate	SE	*p*-Value	Estimate	SE	*p*-Value
Gestational age	0.03591	0.00739	< .0001	0.01626	0.00621	0.0106
Mother's age	−0.00444	0.00504	0.381	−0.01359	0.00424	0.0019
Weight %	0.00097	0.00172	0.5739	0.00016	0.00144	0.9123
Head circumference %	0.000282	0.00147	0.8485	3.9E-05	0.00124	0.9749
Day blood collected	−0.01774	0.0146	0.228	−0.00612	0.01228	0.6195
	DHA composition (wt:wt%)			**ARA composition (wt:wt%)**		
Parameter	Estimate	SE	*p*-Value	Estimate	SE	*p*-Value
Gestational age	0.0419	0.00527	< .0001	0.02224	0.00382	< .0001
Mother's age	0.00764	0.0036	0.037	−0.00151	0.00261	0.5643
Weight %	0.00127	0.00123	0.3036	0.000459	0.000887	0.6061
Head circumference %	0.00151	0.00105	0.1544	0.00127	0.000759	0.0994
Day blood collected	−0.01765	0.01043	0.0942	−0.00604	0.00755	0.4261

* Parameter estimates for data with a natural logarithm transformation.

Our present study sheds important light on these remaining questions by using two metrics to measure LCPUFA status: percent composition and concentration. The former has been the traditional means of expressing FA status, but in theory, *composition* may be markedly biased by artificial dilution with administration of intravenous lipid emulsions. Confirming lower LCPUFA *concentrations* (which would not be affected by the presence of infused precursor FAs) provides strong and independent confirmation that ARA and DHA levels are indeed lower in premature infants. Because concentrations of ARA were lower, it is also unlikely that competition (from infused LA) for the shared synthesis pathway is the cause of low DHA levels in premature infants.

Alternative explanations may include reasons that are unique to premature infants including very low adipose stores, an early catabolic energy state, increased tissue needs for rapid growth/development or decreased function of the shared enzymatic pathway of LCPUFA synthesis from precursor FAs. We demonstrated that total circulating FA concentrations were not higher in preterm compared to term infants. This suggests that premature infants rapidly clear intravenous lipids from circulation. This is

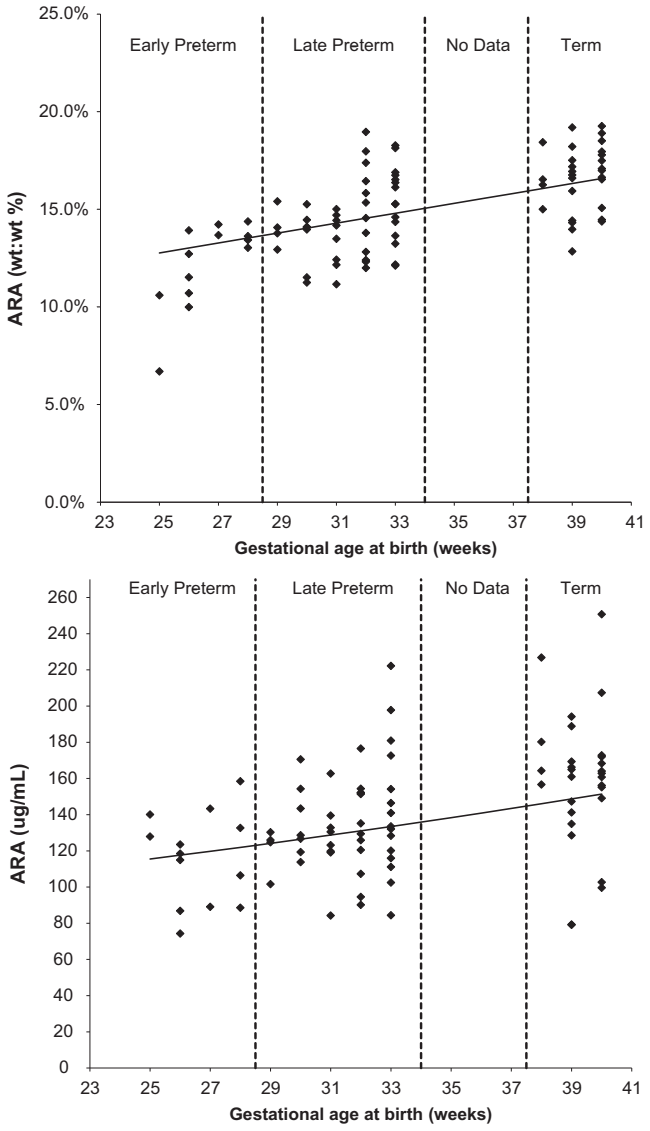

Fig. 1. Relationships between gestational age and blood arachidonic acid (ARA) levels expressed as a composition or percent of total blood fatty acids (top) and as a concentration (bottom).

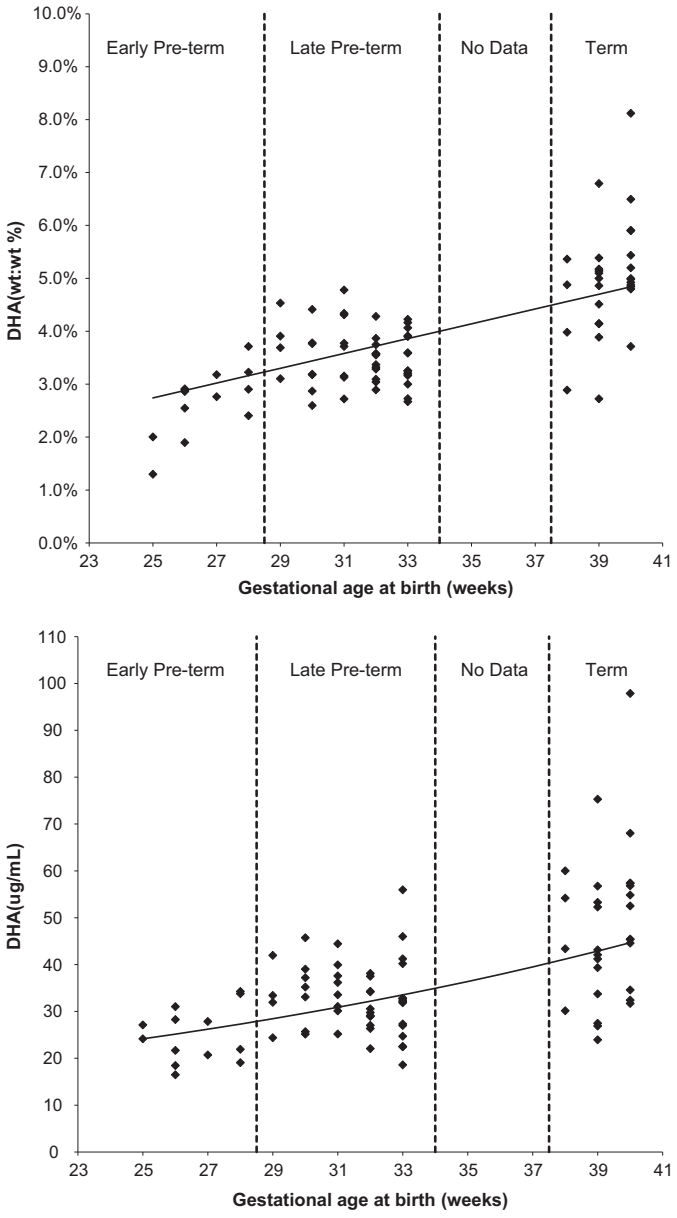

Fig. 2. Relationships between gestational age and blood docosahexaenoic acid (DHA) levels expressed as a composition or percent of total blood fatty acids (top) and as a concentration (bottom).

consistent with clinical practice findings in our NICU where intravenous lipid infusions are not routinely advanced if serum triglyceride levels are significantly elevated (an uncommon event). This finding may also explain why the FA composition and concentration data were consistently associated. The observation that some or both of the immediate metabolic products of LA (elongation, C20:2n6 and Δ-6 desaturation, C18:2n6 and C18:3n6) are elevated in preterm babies, but all subsequent metabolites, (C20:3n6 through C22:5n6) are lower suggests a "blockade" in the production of C20:3n6 (dihomo-gamma-linolenic acid) is present in premature infants (Fig. 3). If so, then provision of both preformed ARA and DHA may be necessary for very premature infants.

4.2. Strengths and limitations

Significant strengths of this study include that it followed adaptive enrollment methods to assure that the study included infants in different GA groups over the same time period. The term reference group excluded both IDM and SGA neonates who reportedly have altered maternal-fetal LCPUFA transport. We used whole blood, which can be seen as a surrogate for all circulating FA fractions (plasma and cells), a validated dried blood spot method of collection for improved study logistics, and we reported FA status in both percent composition and concentration terms. In doing so, we demonstrated that FA profiles, both percent composition and concentration, can be obtained from one drop of scavenged blood, allowing the assessment of FA status in premature infants without additional painful procedures or blood collection. This is beneficial because neonates, especially very low birth weight infants, have a very limited blood volume with a higher risk of anemia, which can hinder serial blood sampling for research. Cord blood samples are generally easier to obtain without detrimental effects to the infant, but may not exclusively represent infant status [34,35].

Weaknesses include the lack of information on maternal dietary and supplementation habits. Clearly, higher maternal intake of DHA (whether from fish or supplements) can influence newborn blood DHA levels [36]. Also this was a single-center study that

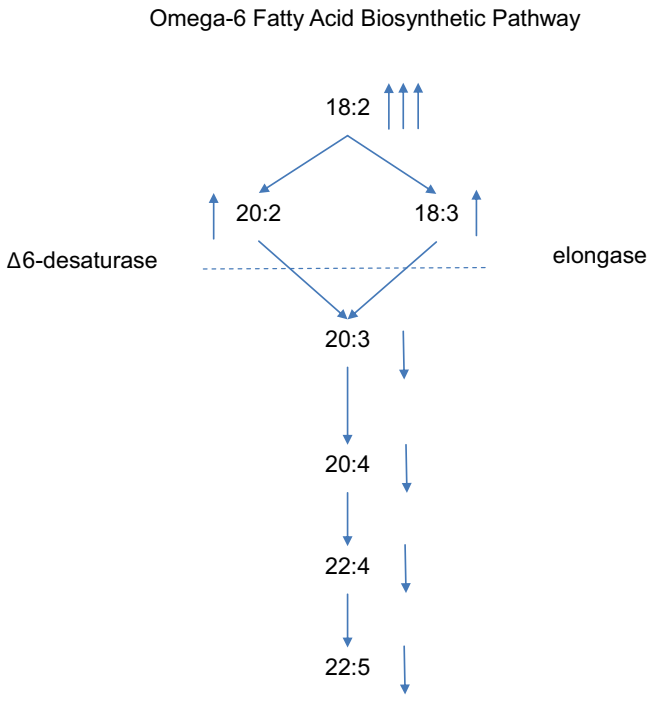

Fig. 3. Apparent point of inhibition of omega-6 LCPUFA synthesis in premature infants (arrows indicate how FA levels in premature infants compare with those in term infants).

took place in the upper Midwest, where fish intake is typically minimal and mother's milk DHA levels are very low [37]. This feature might actually be advantageous in exploring normal LCPUFA physiology relatively independent of diet.

5. Conclusion

This study sheds light on existing questions and advances the understanding of differences in essential FA status between preterm and term infants. We found that GA directly correlates with both ARA and DHA levels in the first week of life, so that infants born at the lowest GA are at the highest risk of deficiency. Additional findings suggest that due to impaired biosynthesis, premature infants have the need for preformed LCPUFAs rather than precursor essential FAs that are currently provided. Knowledge gained adds to a growing platform aimed at tailoring nutritional provision for the very premature infant with the hopes of improving both short- and long-term outcomes.

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Summary

Long chain polyunsaturated fatty acids (LCPUFA) including docosahexaenoic acid (DHA) and arachidonic acid (ARA) are increasingly transferred from mother to fetus late in pregnancy to support rapid growth. Infants born before this transfer is complete are at risk for deficiency. This study determines the relationship between gestational age (GA) and LCPUFA status to better understand the unique needs of premature infants. Whole blood was collected within the first week of life from 60 preterm (<34 weeks GA) and 30 term infants (>38 weeks GA). Both fatty acid (FA) composition and concentration were analyzed and compared, and the association between GA and LCPUFA status was examined. Preterm infants had significantly lower DHA and ARA levels than term peers and levels directly correlated with GA ($p<0.0001$). This study confirms that those babies born the earliest are at the greatest risk of LCPUFA deficiency.

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