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Fatty acids in the placenta of appropiate- versus small-for-gestational-age infants at term birth

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ABSTRACT

Introduction: Fatty acids are essential nutrients for the fetus and are supplied by the mother through the placenta. Desaturase and elongase enzymes play an important role in modulating the fatty acid composition of body tissues. We aimed to compare the fatty acid profile and the estimated desaturase and elongase activities in the placenta of appropriate (AGA) versus small-for-gestational-age (SGA), and to determine their relationship with the offspring size at birth.

Methods: The placental fatty acid profile was analyzed by gas chromatography in 84 infants (45 AGA and 30 SGA) from a prenatal cohort study. The estimated desaturase and elongase activities were calculated from product-precursor fatty acid ratios. Results were associated with maternal (age, body mass index and weight gain during gestation) and neonatal (gestational age, sex, birth weight and birth length) parameters.

Results: Differences in placental fatty acid composition between AGA and SGA infants rather than correlations thereof with neonatal parameters were observed. Placentas from SGA infants contained lower levels of omega-3 (ALA, EPA, DPA, and DHA) and high omega-6/omega-3 ratios (AA/DHA and LA/ALA), as well as low elongase (Elovl5) and high desaturase (D9Dn7 and D5Dn6) activity as compared to AGA infants (all $p < 0.0001$).

Discussion: Placentas of AGA and SGA infants differed in fatty acids profile as well as in estimated desaturase and elongase activities. A striking feature of SGA placentas was the low availability of omega-3. Hence, omega-3 fatty acid status deserves further attention, as a potential target of prenatal interventions.

1. Introduction

Between 5-10% of infants born at term are small for gestational age (SGA). The SGA condition is associated with a higher risk of adverse outcomes during pregnancy, labor, and the neonatal period [1,2], which contribute to neurodevelopmental and metabolic disorders in these subjects [3,4]. Approximately 90% of SGA infants experience spontaneous postnatal catch-up growth, which, when rapid and pronounced, can predispose to insulin resistance, accumulation of central adiposity, early and rapidly evolving puberty, and increased risks of developing

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type 2 diabetes and cardiovascular disease later in life [5–7]. Most cases of low birth weight and/or length result from defective placental function and failure to meet the nutritional requirements of the fetus to support adequate growth [8].

During the last trimester of pregnancy, fetal requirements for long-chain polyunsaturated fatty acids (LC-PUFA) are high [9]. LC-PUFA are important constituents of cell membranes and provide the precursors for eicosanoid production [9], which are needed for the normal development of the nervous and vascular systems [10]. There are two types of essential PUFAs, omega-6 (n6) and omega-3 (n3). Omega-6 fatty acids are represented by linoleic acid (18:2n6, LA) and omega-3 fatty acids by alpha-linolenic acid (18:3n3, ALA). Both essential fatty acids are metabolized to longer-chain fatty acids of 20 and 22 carbon atoms. LA is metabolized to arachidonic acid (20:4n6, AA) and ALA is metabolized to eicosapentaenoic acid (20:5n3, EPA) and docosahexaenoic acid (22:6n3, DHA) [11]. Since the fetus cannot efficiently synthesize these fatty acids [12], fetal essential fatty acids (EFAs) and their long-chain derivatives are supplied by the mother through the placenta [13]. Several authors have suggested that both maternal and umbilical cord PUFAs influence body adiposity and cardiometabolic health of the offspring [14–17].

Besides dietary intake of fatty acids, the activity of the desaturase and elongase enzymes play an important role in modulating the fatty acid composition of body tissues [18]. Although direct measurement of the enzyme activity is difficult, it can be estimated from the product-precursor ratio [19,20]. The elongases of very long-chain fatty acid (ELOVL) are essential in the biosynthesis of fatty acids longer than 14 carbons [21]. The delta-9-desaturases (D9D) catalyze the desaturation of 12–19 carbon saturated fatty acids (SFA) to monounsaturated fatty acids (MUFA) and both the delta-6-desaturase (D6D) and delta-5-desaturase (D5D), catalyze the rate-limiting steps in the conversion of the n6 and n3 PUFA (LA and ALA) to their long-chain metabolites (AA and EPA), respectively [22]. The activity of these enzymes is regulated by nutrient and hormone status and has shown to be associated with obesity and cardiometabolic risk factors in adult tissues [23–25].

Altered composition of circulating fatty acids has been reported in mothers and infants with growth restriction [26–30], including a lower fetal-to-maternal proportion of the LC-PUFA (AA and DHA) and reduced conversion ratios from their derivatives (LA and ALA). In the placenta, a similar fatty acid profile was observed between normal and restricted groups, but the proportion of fatty acids of the linoleic acid series (n6) and the conversion ratio of DHA from its precursor LA (n3) was significantly lower in the restricted placenta compared to the normal placenta [28,31]. Several studies in premature infants showed that smaller size at birth was related to lower EFA concentrations in the infant [32–35]. Knowledge about the fatty acid composition and the activity of the desaturase and elongase enzymes in placentas from SGA term neonates is scarce. We hypothesize that the placental fatty acid profile and the estimated enzymatic activity will be different between SGA and AGA term neonates, and will associate with offspring size at birth.

The present study, therefore, aims to compare the fatty acid profile and the estimated desaturase and elongase activities from placentas of AGA versus SGA infants at term birth, and to determine their relationship with the offspring size at birth.

2. Material and methods

2.1. Study population and ethics

The study cohort consisted of 84 mother-newborn pairs recruited at the Hospital Dr. Josep Trueta of Girona and the Hospital Sant Joan de Déu of Barcelona (Spain) within a prenatal cohort study of mothers and infants. Fifty-four infants were born AGA (21 girls, 33 boys) and 30 SGA (14 girls, 16 boys). The inclusion criteria were: (i) infants born at term (37–42 weeks) from singleton pregnancies, (ii) placentas collected at delivery, and (iii) informed written consent obtained. The exclusion criteria were: (i) maternal disease (hypertension, preeclampsia, gestational diabetes, or preexisting type 1 and type 2 diabetes mellitus), alcohol abuse or drug addiction, and (ii) fetal malformations or complications at birth.

The study was approved by the Institutional Review Board of the Hospital Dr. Josep Trueta of Girona and the Hospital Sant Joan de Déu at the University of Barcelona. Written informed consent was obtained before delivery.

2.2. Clinical assessments

Maternal age at conception, height, pregestational weight, and gestational weight gain, were retrieved from medical records. Body-mass index (BMI) was calculated as weight/height squared (kg/m^2).

Weight and length of the newborns were measured after delivery and are shown here as standard deviation scores (Z-score) adjusting for gestational age and sex according to regional normative data. Gestational age was calculated from last menses and was confirmed by ultrasound when needed. Children with birth weight Z-score ≤ -2 were classified as SGA and children with $-0.5 \leq$ birth weight Z-score $\leq +0.5$ were classified as AGA.

The placentas were collected after childbirth in the delivery room and processed immediately. Placentas were weighed and three 1 cm^3 cuboidal sections were collected from the maternal side of the placenta after removing the decidua. Placental samples were washed 3 times with physiological saline to remove all maternal blood and immediately were frozen at −80 °C until analyzed. The personnel were wearing facial masks and sterile gloves and were also using a sterile scalpel and instruments.

2.3. Placental fatty acid profile and estimated indices

Percentages of total fatty acids from placental lipids (including glycerolipids, phospholipids, sphingolipids, sterol lipids and free fatty acids) were analyzed as fatty acid methyl ester derivatives (FAMEs) by gas chromatography (GC) as previously described [36]. Lipids from placental samples (containing 500 mg of tissue) were extracted with chloroform/methanol (2:1, v/v) in the presence of 0.01% butylated hydroxytoluene. The chloroform phase was evaporated under nitrogen, and the fatty acids were trans-esterified by incubation in 2 ml of 5% methanolic HCl at 75 °C for 90 min. The resulting fatty acid methyl esters were extracted by adding 2 ml of n-pentane and 1 ml of saturated NaCl solution. The n-pentane phase was separated, evaporated under nitrogen and redissolved in 80 μl of carbon disulphide. A total amount of 4 μl was used for GC analysis. Separation was performed with a DBWAX capillary column (30 m × 0.25 mm x 0.20 μm) in a GC System 7890A with a Series Injector 7683B and a FID detector (Agilent Technologies, Barcelona, Spain). Identification of fatty acid methyl esters was made by comparison with authentic standards (Larodan Fine Chemicals, Malmö, Sweden). Results are expressed as mol%.

The following fatty acyl indices were calculated: saturated fatty acids (SFA); monounsaturated fatty acids (MUFA); polyunsaturated fatty acids (PUFA) from n3 and n6 series (PUFAn3 and PUFAn6, respectively); and the following ratios were obtained: PUFAn6/PUFAn3, LA(n6)/ALA(n3), AA(n6)/DHA(n3), LA + AA n6 score, ALA + DHA n3 score, AA(n6)/LA (n6) and DHA(n3)/ALA(n3).

Desaturase and elongase activities were estimated from specific product-precursor fatty acid ratios: D9Dn7 = 16:1n9/16:0; D9Dn9 = 18:1n9/18:0; D6Dn3 = 18:4n3/18:3n3, D5Dn6 = 20:4n6/20:3n6; D4Dn6 = 22:5n6/22:4n6; D4Dn3 = 22:6n3/22:5n3; Elovl3 = 20:1n9/18:1n9; Elovl6 = 18:0/16:0; Elovl1a = 20:0/18:0; Elovl1b = 22:0/20:0; Elovl1c = 24:0/22:0; Elovl5 = 20:2n6/18:2n6; Elovl2n6 = 22:4n-6/20:4n-6 and Elovl2n3 = 22:5n-3/20:5n-3.

2.4. Statistical analysis

Descriptive characteristics are shown as mean ± SEM. Statistical analyses were performed using SPSS Statistics 22.0 (SPSS, Chicago, IL). For variables with non-normal distribution, data were logarithmically transformed before analyses. Unpaired *t*-test was used to study differences between AGA and SGA subgroups. The level of significance was set at $p \leq 0.05$. Bivariate correlations were done to study the associations between the placental fatty acid profile and offspring birth weight and birth length. Multiple linear regression analyses were performed to correct by maternal (age, BMI, gestational weight gain) and neonatal (gestational age and sex) confounders.

3. Results

3.1. Maternal and newborns' characteristics

Table 1 summarizes the anthropometric parameters of the mothers and newborns by birth weight subgroup. There were no differences between the groups regarding maternal age at conception, pregestational weight and BMI, gestational weight gain, and newborns' sex. As expected, SGA infants at birth were smaller than AGA children, and they did also have smaller placentas (all $p < 0.0001$).

3.2. Placental fatty acid profile

Comparisons of placental fatty acid profiles from AGA and SGA subgroups are shown in Table 2. The percentage of total fatty acids indices was similar between both groups although there were some differences within individual fatty acids mainly from the omega-3 and omega-6 series. Placentas from SGA infants contained lower levels of several PUFAn3 including alpha-linolenic acid (ALA, 18:3n3), eicosapentaenoic acid (EPA, 20:5n3), docosapentaenoic acid (DPA, 22:5n3) and docosahexaenoic acid (DHA, 22:6n3) (all $p < 0.0001$). The ALA + DHA n3 score and the total PUFAn3 was also significantly lower in SGA than in AGA infants ($p < 0.0001$ and $p = 0.04$, respectively). On the other hand, higher levels of LA + AA n6 score ($p = 0.04$) and also of the different omega-6/omega-3 ratios (PUFAn6/PUFAn3, LA/ALA and AA/DHA) were observed in SGA infants (all $p < 0.0001$). Fig. 1A shows the differential fatty acids among AGA and SGA expressed as SGA Z-scores using the AGA mean as reference.

None of these fatty acids were associated with birth weight or length of the infants (not shown). However, the differences in placental fatty acid composition between AGA and SGA infants were maintained in multivariate analyses adjusted for maternal (age, BMI, gestational weight gain) and neonatal (gestational age and sex) characteristics.

Table 1
Characteristics of the studied population.

	AGA (n = 54)	SGA (n = 30)	P value
Mothers			
Age (yr)	31.0 ± 0.5	30.3 ± 1.1	Ns
Height (cm)	163.1 ± 0.7	159.5 ± 1.13	0.009
Weight (Kg)	58.8 ± 0.7	57.33 ± 1.7	Ns
BMI (Kg/m^2)	22.1 ± 0.2	22.60 ± 0.7	Ns
Gestational weight gain (Kg)	11.6 ± 0.3	11.5 ± 0.9	Ns
Newborns			
Sex (%F)	40	46	Ns
Gestational age (weeks)	39.6 ± 0.1	38.2 ± 0.2	<0.0001
Placental weight (Kg)	0.58 ± 0.01	0.46 ± 0.01	<0.0001
Birth weight (Kg)	3.26 ± 0.03	2.22 ± 0.05	<0.0001
Birth weight Z-score	−0.03 ± 0.08	−2.36 ± 0.06	<0.0001
Birth length (cm)	49.41 ± 0.20	44.80 ± 0.38	<0.0001
Birth length Z-score	−0.22 ± 0.12	−2.12 ± 0.13	<0.0001

Data are mean ± SEM. *t*-test was used to determine differences between groups. Ns, not significant.

Table 2
Placental fatty acid profile in the studied population.

	AGA (n = 54)	SGA (n = 30)	P value
Fatty acids			
14:0 (Myristic acid)	1.81 ± 0.06	1.68 ± 0.06	Ns
16:0 (Palmitic acid)	33.81 ± 0.36	33.87 ± 0.33	Ns
18:0 (Stearic acid)	17.32 ± 0.21	17.12 ± 0.22	Ns
20:0 (Arachidic acid)	0.33 ± 0.01	0.32 ± 0.01	Ns
22:0 (Behenic acid)	1.59 ± 0.12	1.39 ± 0.13	Ns
24:0 (Lignoceric acid)	0.38 ± 0.05	0.15 ± 0.01	0.004
Total SFA	55.14 ± 0.55	54.55 ± 0.43	Ns
16:1n7 (Palmitoleic acid)	0.49 ± 0.01	0.59 ± 0.02	**0.001**
18:1n7 (Vaccenic acid)	2.03 ± 0.03	1.91 ± 0.03	**0.02**
18:1n9 (Oleic acid)	12.29 ± 0.23	12.13 ± 0.29	Ns
20:1n9 (Eicosenoic acid)	0.26 ± 0.01	0.28 ± 0.01	Ns
22:1n9 (Erucic acid)	0.75 ± 0.07	0.97 ± 0.04	0.04
Total MUFA	15.92 ± 0.29	15.97 ± 0.36	Ns
18:3n3 (Alpha-linolenic acid, ALA)	0.22 ± 0.01	0.15 ± 0.01	**<0.0001**
18:4n3 (Stearidonic acid)	0.84 ± 0.08	0.71 ± 0.03	Ns
20:3n3 (Eicosatrienoic acid)	3.05 ± 0.14	3.39 ± 0.14	Ns
20:5n3 (Eicosapentaenoic acid, EPA)	0.84 ± 0.03	0.61 ± 0.02	**<0.0001**
22:5n3 (Docosapentaenoic acid, DPA)	0.23 ± 0.01	0.15 ± 0.01	**<0.0001**
22:6n3 (Docosahexaenoic acid, DHA)	1.04 ± 0.07	0.61 ± 0.02	**<0.0001**
Total PUFAn3	6.22 ± 0.16	5.65 ± 0.14	**0.02**
18:2n6 (Linoleic acid, LA)	9.53 ± 0.20	10.18 ± 0.26	0.04
20:2n6 (Eicosadienoic acid)	0.11 ± 0.01	0.05 ± 0.01	**<0.0001**
20:3n6 (Dihomo-gamma-linolenic acid, DGLA)	0.56 ± 0.01	0.51 ± 0.02	0.04
20:4n6 (Arachidonic acid, AA)	11.31 ± 0.53	12.58 ± 0.46	Ns
22:4n6 (Adrenic acid)	0.49 ± 0.02	0.30 ± 0.01	**<0.0001**
22:5n6 (Osbond acid)	0.11 ± 0.07	0.11 ± 0.01	Ns
Total PUFAn6	22.42 ± 0.63	23.82 ± 0.45	Ns
PUFAn6/PUFAn3	3.58 ± 0.08	4.27 ± 0.11	**<0.0001**
LAn6/ALAn3	44.67 ± 2.11	74.48 ± 5.3	**<0.0001**
AAn6/DHAn3	12.37 ± 0.68	21.35 ± 1.12	**<0.0001**
LA + AA n6 score	20.70 ± 0.70	22.77 ± 0.47	0.04
ALA + DHA n3 score	1.26 ± 0.07	0.76 ± 0.02	**<0.0001**
AAn6/LA n6	1.19 ± 0.04	1.26 ± 0.06	Ns
DHAn3/ALAn3	5.27 ± 0.53	4.48 ± 0.34	Ns
Estimated desaturase and elongase			
D9Dn7	0.015 ± 0.01	0.017 ± 0.01	**0.001**
D9Dn9	0.70 ± 0.01	0.71 ± 0.02	Ns
D6Dn3	3.65 ± 0.31	4.97 ± 0.24	0.005
D5Dn6	19.73 ± 0.81	26.81 ± 1.85	**<0.0001**
D4Dn6	0.24 ± 0.02	0.37 ± 0.02	<0.0001
D4Dn3	5.35 ± 0.33	4.37 ± 0.27	Ns
Elovl3	0.022 ± 0.01	0.023 ± 0.01	Ns
Elovl6	0.52 ± 0.01	0.50 ± 0.01	Ns
Elovl1a	0.019 ± 0.01	0.018 ± 0.01	Ns
Elovl1b	4.52 ± 0.29	4.20 ± 0.25	Ns
Elovl1c	0.56 ± 0.10	0.13 ± 0.01	0.005
Elovl5	0.014 ± 0.01	0.006 ± 0.01	**<0.0001**
Elovl2n6	0.06 ± 0.01	0.03 ± 0.01	0.007
Elovl2n3	0.30 ± 0.01	0.26 ± 0.02	Ns

Data are mean ± SEM. *t*-test was used to determine differences between groups. Ns, not significant. The estimated desaturase and elongase activities were calculated from product-precursor fatty acid ratios. Significant differences after adjustment for maternal (age, BMI, gestational weight gain) and neonatal (gestational age and sex) characteristics are shown in bold.

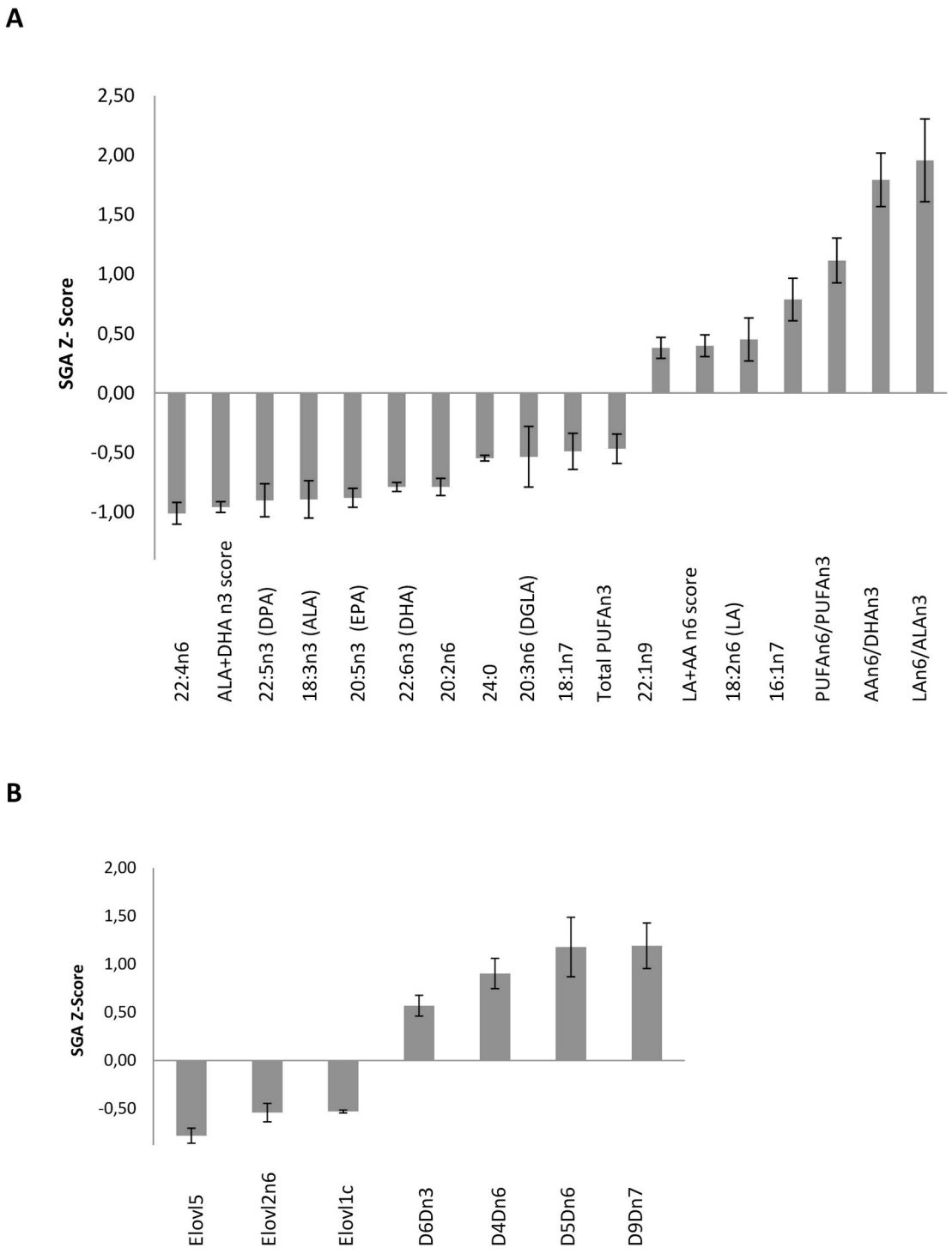

Fig. 1. Differential placental fatty acids (A) and estimated desaturase and elongase activities (B) in SGA infants (expressed as Z-scores using the AGA results as reference). Negative values indicate lower levels than AGA and positive values indicate higher levels than AGA.

3.3. Estimated desaturase and elongase activity

Comparisons of the estimated desaturase and elongase activities from AGA and SGA subgroups are shown in Table 2. Placentas from SGA infants showed higher desaturase (D9Dn7, D6Dn3, D5Dn6 and D4Dn6) and lower elongase (Elovl1c, Elovl5, Elovl2n6) activity (all $p < 0.007$). Differential desaturase and elongase activities are shown in Fig. 1B that depicts the enzymatic activities of SGA as Z-scores, using the AGA results as reference.

None of the estimated activities were associated with birth weight or length of the infants (not shown). However, the differences in placental desaturase and elongase activities between AGA and SGA infants were maintained in multivariate analyses adjusted for maternal (age, BMI, gestational weight gain) and neonatal (gestational age and sex) characteristics.

4. Discussion

We described, for the first time to our knowledge, the fatty acid profile and the estimated desaturase and elongase activities in placentas

from AGA and SGA term neonates. Placentas from SGA infants showed low levels of omega-3 and high omega-6/omega-3 ratio, and high desaturase (D9Dn7 and D5Dn6) and low elongase (Elovl5) activity compared to AGA infants.

Only two studies had previously examined the impact of fetal growth restriction on fatty acids profile in human placenta. Percy et al. (1991) studied the essential fatty acids pattern in placentas from AGA pregnancies (n = 7) and from preterm and term SGA (n = 15), and showed a reduction of n-6 series (including 20:3 and 20:4) in acylglycerol and phosphatidylcholine fatty acids from SGA placentas [31]. Assumpçao et al. (2017) investigated the profile of LC-PUFA in placentas from 15 full-term normal pregnancies (AGA) and 11 pregnancies complicated by intrauterine growth retardation, and showed no significant differences in any of the studied fatty acids; however, DHA/ALA (n3) ratio was significantly lower in the IUGR group [28]. Our study has been performed with a higher number of subjects and all infants (both AGA and SGA) were born at term.

An impaired ability of the placenta to supply derivatives of LA and ALA from their precursors (AA and DHA, respectively) has been described in infants with growth restriction, most of them being premature, compared to control subjects [26,27,31,34]. However, in our study with term SGA newborns, no significant differences were observed in the conversion ratios AA/LA (n6) and DHA/AA (n3) but rather in the levels of PUFAn6/PUFAn3 ratios, suggesting that the main differences between AGA and SGA newborns at term birth are due to an imbalance between omega-6 and omega-3 PUFA levels.

Experimental studies have suggested that omega-6 and omega-3 fatty acids participate in the regulation of lipid metabolism and systemic inflammation eliciting opposing effects [37,38]. While a high omega-6/omega-3 ratio has been associated with a pro-inflammatory role and the pathogenesis of many diseases, including cardiovascular disease, cancer, obesity and autoimmune diseases; increased levels of omega-3 PUFA (a low omega-6/omega-3 ratio) has shown to exert anti-inflammatory effects and to protect against cardiometabolic diseases [39]. On the basis of these findings, and given that the fatty acid composition of the placenta showed a comparable pattern to neonatal venous plasma [40], we speculate that the increased omega-6/omega-3 ratio and the decreased omega-3 PUFA levels observed in SGA placentas could possibly contribute to the increased risk of cardiometabolic disorders described in later stages of SGA infants' life. In this sense, lower PUFAn3 and higher PUFAn6 levels during pregnancy were associated with impaired metabolic status in the offspring at age 6 yr [15,16]. In a rat model, high omega-6/omega-3 exposure during perinatal development regulates offspring adipogenic potential and conditions adult obesity resistance [41].

The endogenous fatty acid synthesis is regulated by elongation and desaturation enzymes [18]. Our results showed that placentas from SGA children had higher D9Dn7 and D5Dn6 activities and lower Elovl5 activity. D9Dn7, also known as stearoyol-CoA desaturase-1 (SCD1), catalyzes the desaturation of palmitic acid (C16:0) to its monounsaturated counterpart, palmitoleic acid (C16:1). Translational evidence suggests that SCD1 plays a pivotal role in regulating lipid and metabolic homeostasis [42]. SCD1 activity has been positively associated with obesity, insulin resistance, and dyslipidemia in human and mouse models [43–45]. D5Dn6, which is required for the synthesis of LC-PUFA, has also been associated with obesity and insulin resistance in children [24]. Elovl5 is a condensing enzyme involved in the elongation of a broad range of fatty acids including ALA, AA and EPA [46]. It has been described as an essential enzyme for hepatic lipid metabolism and the deletion of Elovl5 causes hepatic steatosis in mice [47]. Elovl5 has also been identified as an epigenetic mark for the risk of type 2 diabetes mellitus [48]. Together, these data indicate that placentas from SGA infants displayed an altered regulation of fatty acid desaturation and elongation activities that have been related to metabolic disturbances in several studies. Experimental data showed that enzymatic activity can be regulated by omega-3 and omega-6 fatty acids levels [49–51]. We propose that the high transfer of maternal dietary omega-6 fatty acids across the placenta could inhibit the expression and activity of fatty acid desaturases required for the synthesis of long-chain n-3 and n-6 fatty acids, leading to fetal growth restriction. An increased desaturase activity might benefit the fetus by the achievement and maintenance of fetal tissue n-3 and n-6 fatty acid patterns. Fatty acid synthesis/metabolism are known to vary in different organs since there is a differential demand of individual tissues for specific fatty acids [52].

On the basis of these findings, we speculate that the differential fatty acid composition noted in SGA placentas could lead to alterations in fatty acid transport of essential nutrients to the fetal compartment and contribute to the increased cardiometabolic risk described in SGA infants; however, additional longitudinal studies will be necessary to address this issue. Moreover, recent data showed that GRP20, an omega-3 fatty acid receptor that mediates anti-inflammatory and insulin-sensitizing effects [53], is overexpressed in SGA placentas [54]. Hence, PUFAn3 and their mediating receptors deserve further attention as potential targets of prenatal interventions.

We acknowledge several limitations in our study. The fatty acid profile was not assessed in maternal or fetal blood. The advantage of using placenta is that it is a spare tissue at birth available for sample collection. Moreover, while the concentration of lipids in blood varies according to its local synthesis and influx into the circulation, and its absorption from dietary sources and efflux over time; the concentration of the lipids in tissues remains more stable [55]. Another concern is that while others have studied the fatty acid profile by lipid classes (triglycerides, phospholipids, cholesteryl ester and NEFA) we have studied the total lipid content of the placenta. Future studies addressing the lipid classes would provide further information on their specific role in the placenta. Another limitation is the lack of maternal dietary intake questionnaires that would be useful to know whether the low level of omega-3 fatty acids present in the SGA placentas is due to a low maternal intake and/or dysregulated placental function. Finally, because elongase and desaturase activities are difficult to measure, the ratios of product-precursor fatty acid pairs were used as a surrogate [56,57]. We recognize that apart from the elongase and desaturase activities themselves, other factors including maternal diet, maternal metabolism, selective placental uptake and selective placental metabolism might influence these ratios. The strength of our methodology is that it eases the clinical implementation as no previous sorting or isolation would be required.

In conclusion, our data show that placentas of AGA and SGA infants differed in fatty acid profile (low omega-3 and high omega-6/omega-3) as well as in desaturase and elongase activities (high D9Dn7 and D5Dn6 and low Elovl5). The omega-3 fatty acid status may represent a modifiable factor related to SGA condition in infants born at term.

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Author contribution

AGV and BMP: contributed to the design and data collection and drafted the manuscript; MD and ABS: contributed to sample and data collection and reviewed the manuscript; SXT, GCB: contributed to data analysis and reviewed the manuscript; JM and MMG performed the fatty acid analysis; FdZ and LI: contributed to the data interpretation and reviewed the manuscript; JB and ALB: contributed to study design, data analysis and interpretation and reviewed the manuscript.

Declaration of competing interest

None of the authors has any potential conflict of interest, real or perceived regarding this work.

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