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Hypertriglyceridemia and lipid tolerance in preterm infants with a birth weight of less than 1250 g on routine parenteral nutrition

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Clinical Nutrition

# Hypertriglyceridemia and lipid tolerance in preterm infants with a birth weight of less than 1250 g on routine parenteral nutrition

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| **Abstract:** | Objectives<br><br>To study the association of hypertriglyceridemia and of lipid tolerance with clinical and nutritional data in preterm infants receiving routine parenteral nutrition.<br><br>Design<br><br>We retrospectively studied 672 preterm infants (gestational age <32 weeks) with birth weight <1250 g, consecutively admitted to our NICU, born between 2004 and 2018. Selected prenatal data and interventions, parenteral intakes and diseases were considered. Hypertriglyceridemia was defined as plasma triglycerides > 250 mg•dL -1 . Lipid tolerance was defined as the ratio of plasma triglycerides to the intravenous lipid intake at the time of sampling. Variables associated to hypertriglyceridemia and to lipid tolerance were identified by multiple logistic and linear regression analyses.<br><br>Results<br><br>Hypertriglyceridemia occurred in 200 preterm infants (30%), ranging from 67% at 23 weeks to 16% at 31 weeks' gestation. In 138 infants (69%) hypertriglyceridemia occurred at a lipid intake of 2.5 g•kg -1 or less. Lipid tolerance was reduced especially in infants of less than 28 weeks' gestation (14.3±9.3 vs 18.8± 10.2, respectively, p<0.001). Lipid tolerance was negatively associated with respiratory distress syndrome (OR= -1.14, p=0.011), patent ductus arteriosus (OR= -1.73, p<0.001), small for gestational age (OR= -2.96, p<0.001), intraventricular haemorrhage (OR= -3.96, p<0.001), late onset sepsis (OR= -8.56, p=0.039).<br><br>Conclusion<br><br>Preterm infants on routine parenteral nutrition were able to tolerate markedly lower |

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| | intravenous lipid intakes than the recommended target values of current guidelines. Lipid tolerance was associated with some of the major complication of prematurity, possibly at risk of developing hypertriglyceridemia. |

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**TITLE PAGE**

# Hypertriglyceridemia and lipid tolerance in preterm infants with a birth weight of less than 1250 g on routine parenteral nutrition

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Short running head: Blood triglycerides and triglyceride metabolism in preterms

Abbreviations: AA: amino acid; BW: birth weight; DOL: day of life; EOS: early onset sepsis; FO LEs: fish oil lipid emulsions; GA: gestational age; HiTG: hypertriglyceridemia; IV: intravenous; IVH: intraventricular haemorrhage; LOS: late onset sepsis; NICU: neonatal intensive care unit; PDA: patent ductus arteriosus; PN: parenteral nutrition; RDS: respiratory distress syndrome; SGA: small-for-gestational-age; TG: triglycerides.

## ABSTRACT

***Objectives***: To study the association of hypertriglyceridemia and of lipid tolerance with clinical and nutritional data in preterm infants receiving routine parenteral nutrition.

***Design***: We retrospectively studied 672 preterm infants (gestational age <32 weeks) with birth weight <1250 g, consecutively admitted to our NICU, born between 2004 and 2018. Selected prenatal data and interventions, parenteral intakes and diseases were considered. Hypertriglyceridemia was defined as plasma triglycerides > 250 $mg \cdot dL^{-1}$. Lipid tolerance was defined as the ratio of plasma triglycerides to the intravenous lipid intake at the time of sampling. Variables associated to hypertriglyceridemia and to lipid tolerance were identified by multiple logistic and linear regression analyses.

***Results***: Hypertriglyceridemia occurred in 200 preterm infants (30%), ranging from 67% at 23 weeks to 16% at 31 weeks' gestation. In 138 infants (69%) hypertriglyceridemia occurred at a lipid intake of 2.5 $g \cdot kg^{-1}$ or less. Lipid tolerance was reduced especially in infants of less than 28 weeks' gestation (14.3±9.3 vs 18.8± 10.2, respectively, $p<0.001$). Lipid tolerance was negatively associated with respiratory distress syndrome (OR= -1.14, p=0.011), patent ductus arteriosus (OR= -1.73, $p<0.001$), small for gestational age (OR= -2.96, $p<0.001$), intraventricular haemorrhage (OR= -3.96, $p<0.001$), late onset sepsis (OR= -8.56, p=0.039).

***Conclusion***: Preterm infants on routine parenteral nutrition were able to tolerate markedly lower intravenous lipid intakes than the recommended target values of current guidelines. Lipid tolerance was associated with some of the

major complication of prematurity, possibly at risk of developing hypertriglyceridemia.

Keywords: lipid metabolism, hypertriglyceridemia, parenteral nutrition, preterm infants, triglycerides.

## INTRODUCTION

High intravenous (IV) lipid intakes in preterm infants have been associated with elevated plasma triglyceride (TG) concentrations [1, 2]. Current ESPGHAN parenteral nutrition (PN) guidelines for preterm infants [3] recommend a maximum IV lipid intake of 4.0 g $\cdot kg^{-1} \cdot d^{-1}$, while ASPEN [4] advises up to 3.0 $g \cdot kg^{-1} \cdot d^{-1}$. However, there are studies in small preterm infants reporting hypertriglyceridemia (HiTG) already at 2.0 $g \cdot kg^{-1} \cdot d^{-1}$ or less [5, 6].

Plasma TG monitoring is strongly recommended and 200 $mg \cdot dL^{-1}$ (2.3 $mmol \cdot L^{-1}$) or 265 $mg \cdot dl^{-1}$ (3.0 $mmol \cdot L^{-1}$) are the suggested thresholds for lipid titration according to ASPEN and ESPGHAN, respectively [3, 4, 7]. Plasma TG monitoring may decrease IV lipid intake and this, in turn, may result in a lower energy intake, especially for the smallest infants. This remains of concern among neonatologists [8, 9].

Scanty information from small cohorts' studies is available on HiTG and lipid tolerance (LT) during PN in very preterm infants. Moreover, the association between HiTG and concomitant illnesses is often not studied and lipid intake at the time of TG determination is often not available [10-12]. Furthermore, obtaining more information on LT in preterm infants on routine PN could help identifying the ability of infants to clear IV lipids before the development of HiTG.

We sought to study the association of HiTG and of LT with the perinatal characteristics, concomitant diagnoses and the simultaneous IV lipid intakes in a large cohort of small preterm infants on routine PN from birth.

## SUBJECTS AND METHODS

***Study population***: We enrolled all infants consecutively admitted to the NICU of "G. Salesi" Children's Hospital, Ancona (Italy), between 2004 and 2018, with a birth weight (BW) lower than 1250 g and a gestational age (GA) lower than 32 weeks, who routinely received PN from the first hour of life. Exclusion criteria were major congenital malformations, inborn errors of metabolism, admission to the NICU after 24 hours of life, death or transfer to another unit before 10 days of life (DOL) and missing clinical information.

***Nutrition protocol and biochemical monitoring:*** Nutrition protocols and biochemical monitoring policies were established in 2002, and they are still applied at our NICU. Accordingly, study infants with a BW lower than 1250 g received routine PN from the first hours of life. IV lipids were infused at a dose of 1.0-1.5 $g \cdot kg^{-1}d^{-1}$ on the DOL 1 up to 2.5-3.5 $g \cdot kg^{-1}d^{-1}$ on the DOL 5. From DOL 1 to 5, glucose was increased from 6.0-8.0 to 12.0-14.0 $g \cdot kg^{-1}d^{-1}$ and amino acids (AA) from 1.0-1.5 $g \cdot kg^{-1}d^{-1}$ on the DOL 1 up to 2.5-3.5 $g \cdot kg^{-1}d^{-1}$. Maximum IV lipid, AA and glucose intakes were kept constant from DOL 5 to DOL 7. All infants received minimal enteral feeding from DOL 1 to DOL 7. The maximum amount of human milk or infant milk formula were supplied at 8 mL·kg-1·d-1 from DOL 1 to DOL 4, 16 mL·kg-1·d-1 from DOL 5 to DOL 7, and then it was gradually increased. PN was tapered after DOL 7 and stopped when the infant tolerated about 120 $kcal \cdot kg^{-1} \cdot d^{-1}$ orally, generally during the 3rd

week of life. Patients received only one of the 5 lipid emulsions routinely available at our hospital pharmacy, assigned by the attending neonatologist according to pharmacy availability, or sometimes as part of clinical trials conducted in the past in our NICU: Lipidem® 20%, B Braun (50:40 medium chain TG - MCT: Soybean oil, 10% fish oil ), SMOFlipid® 20%, Fresenius Kabi (30:30:25 MCT: soybean oil: olive oil, 15% fish oil), Intralipid® 20%, Fresenius Kabi (100% soybean oil), Lipofundin MCT® 20%, B Braun (50%MCT and 50% soybean oil) and Clinoleic® 20%, Baxter spa (80% olive oil and 20% soybean oil).

Metabolic tolerance was assessed by measuring plasma TG, urea, creatinine and glycaemia using micro-methods (Reflotron® Plus, Sprint system, Roche Diagnostics International Ltd and Accu-chek Aviva Meter, Roche Diabetes Care, Inc.). During the study period HiTG episode was defined as TG concentration greater than 250 $mg \cdot dL^{-1}$; others metabolic complications were defined as previously described [13].

Biochemical TG monitoring was performed on the DOL 3, 5 and 7 and then weekly during PN. Additional determinations might have been performed in selected cases at discretion of the attending physician.

***Data collection and definitions:*** During hospital stay, perinatal characteristics, nutritional and biochemical data were prospectively recorded by the nursing staff and attending neonatologists in the electronic medical record (Neotools; Interactive, Milan, Italy).

Administered IV lipid, AA and glucose intakes ($g \cdot kg^{-1} \cdot d^{-1}$) were calculated hourly using daily weight, PN bag composition and syringe pump rate ($ml \cdot h^{-1}$). GA was estimated by early ultrasound performed in the first trimester of pregnancy. The

major complications of prematurity were defined according to the Vermont Oxford definitions. Asphyxia was defined as cord blood pH less than 7.0 and standard base excess less than -12.0 mmol·$L^{-1}$. Small-for-gestational-age ($SGA^{10th\ centile}$) was defined as a BW less than the $10^{th}$ percentile by using Italian reference growth charts [14].

LT was calculated as the ratio between administered IV lipid intake (g·$kg^{-1}$) and plasma TG concentration (g·$dL^{-1}$), where "administered IV lipid intake" is the mean IV lipid infusion during the 3 hours before TG determination. Patients received parenteral nutrition over 24 hours (continuous infusion) and lipid infusion was not halted before the blood withdrawal.

***Ethics:*** The study was approved by the local ethics committee (ID 447790) and was in accordance with the principles of the Helsinki Declaration as revised in Fortaleza, October 2013.

***Statistical analysis:*** Descriptive analysis was used to describe the study patients. Clinical characteristics, LT, IV lipid intake, plasma TG concentration and incidence of HiTG of the study groups were analysed by using the independent t-test, Mann-Whitney test, Kruskal-Wallis test or Chi square test as appropriate. A p-value of less than 0.05 was considered significant.

Binary logistic regression analysis with the enter method was performed to identify risk factors for HiTG episodes while multiple linear regression analysis with the enter method was used to assess the relationship between LT and clinical characteristics of our cohort of infants. All the TG determinations in the study period for each infant were used. Pearson's correlation test or Chi square test were performed to identify variables significantly associated with HiTG and with LT at univariate analysis. Variables were included in the logistic and linear

regression analyses as independent variables if $p<0.1$ at univariate. All statistical analyses were performed by using SPSS software (v 23.0; SPSS Inc, Chicago, Illinois).

Independent variables for both logistic and linear regression analyses are listed below.

*Perinatal and pregnancy characteristics*: GA (weeks), $SGA^{10th\ centile}$, BW-SDS, gender, exposure to antenatal steroids (any steroids administered to the mother before birth), hypertension in pregnancy (HIP), type of delivery, singleton birth, Apgar score at 5 minutes, surfactant therapy.

*Nutritional therapies*: mean IV lipid intake ($g \cdot kg^{-1}d^{-1}$) administered during the 3 hours before plasma TG measurement, type of IV lipid emulsions and IV AA and glucose ($g \cdot kg^{-1}d^{-1}$) intakes administered during the 24 hours prior to the determination.

*Complications of prematurity*: Neonatal asphyxia, late onset sepsis (LOS), early onset sepsis (EOS), patent ductus arteriosus (PDA), intraventricular haemorrhage (IVH) grade III and IV, necrotizing enterocolitis grade II and III and respiratory distress syndrome (RDS).

Complication of prematurity and nutritional therapies were included in the analysis only when present at the time of TG measurement.

Both in the logistic and in the linear regression analysis the independent variables were considered significantly associated with the dependent variables if p value was lower than 0.05.

## RESULTS

Eight hundred and fifty-one infants with a BW of less than 1250 g and born before 32 weeks' gestation were studied. These infants represent nearly the 100% of the infants with such characteristics born in the Marche Region. One hundred and forty-five infants were excluded: 31 had major malformations, 29 were admitted in the NICU after 24 hours of life, 76 died or were transferred to another unit before DOL 10 and 9 had missing clinical information. Out of 706 patients who met the inclusion criteria, 672 were included, with at least one plasma TG determination before DOL 10 available. The BW and GA of the study infants were (mean±SD) 924±199 g and 28±2 weeks, respectively. Three hundred and twenty-seven infants were born at GA ranging from $23^{0/7}$ to $27^{6/7}$ weeks, whereas 345 infants were born between $28^{0/7}$ and $31^{6/7}$ weeks. Among prenatal factors infants with GA below 28 weeks differed from infants with 28 to 32 weeks' gestation for incidence of HIP, any antenatal steroids therapy and caesarean delivery (HIP: 19% vs 45%; p=0.001; antenatal steroid therapy: 85% vs 90%; p= 0.043; caesarean delivery: 75% vs 95%, p<0.001, respectively). The incidence of several prematurity complications was also significantly different between two GA groups (<28 weeks vs 28 to 32 weeks' gestation : $SGA^{10th\ centile}$: 14% vs 40%, p<0.001; asphyxia: 7% vs 3%, p=0.007; PDA: 73% vs 46%, p<0.001; IVH grade III and IV: 13% vs 1%, p<0.001; RDS: 97% vs 79%, p<0.001).

***Incidence of HiTG, IV lipid intake and LT:*** Two hundred of the 672 infants (30%) exhibited at least one plasma TG concentration higher than 250 $mg \cdot dL^{-1}$. Lower GA was significantly associated with higher incidence of HiTG (p<0.001, **Figure 1A**) as well as with greater plasma TG concentrations (p<0.001, **Figure 1B**). Infants born between $23^{0/7}$ and $27^{6/7}$weeks' gestation showed more than

two-fold increase in the incidence of HiTG levels than infants born at $28^{0/7}$ and $31^{6/7}$ weeks (42% vs 19%; p<0.001).

Administered IV lipid intake was also significantly associated with GA (p<0.001, **Figure 1C**). The mean IV lipid intake ($g \cdot kg^{-1} \cdot d^{-1}$) from day 1 to 3, from day 5 to 7 and from day 8 to 10 in infants born before 28 weeks' gestation and in those who were born between 28 and 32 weeks were: 1.1±0.3 vs 1.1±0.3 (p=0.5), 2.1±0.6 vs 2.3±0.6 (p<0.001), 1.9±0.5 vs 2.1±0.5 (p=0.001), respectively. The mean maximum IV lipid intake during the first 10 DOLs were 2.5±0.5 vs 2.6±0.5 (p=0.010), in infants with a GA lower than 28 weeks and in those with a GA between 28 and 32 weeks respectively.

Sixty-nine per cent (n=138) of the first HiTG episodes in the whole population occurred at IV lipid intake of 2.5 $g \cdot kg^{-1}$ or less.

Two hundred and forty-five patients (37%; 120 with a GA lower than 28 weeks' and 125 with GA between 28 and 32 weeks) received fish oil containing lipid emulsions (FO LEs). The incidence of HITG were significantly lower in infants receiving FOLEs compared to infants receiving conventional IV lipid emulsions (22% vs 34% respectively; p=0.002).

The incidence of HiTG did not change during the 14-year study period (p=0.154, data not shown).

LT was calculated for 1931 samples and it was lower in infants born before 28 weeks' compare to those with a GA between 28 and 32 weeks (14.3±9.3 vs 18.8± 10.2, respectively, p<0.001; **Figure 1D**).

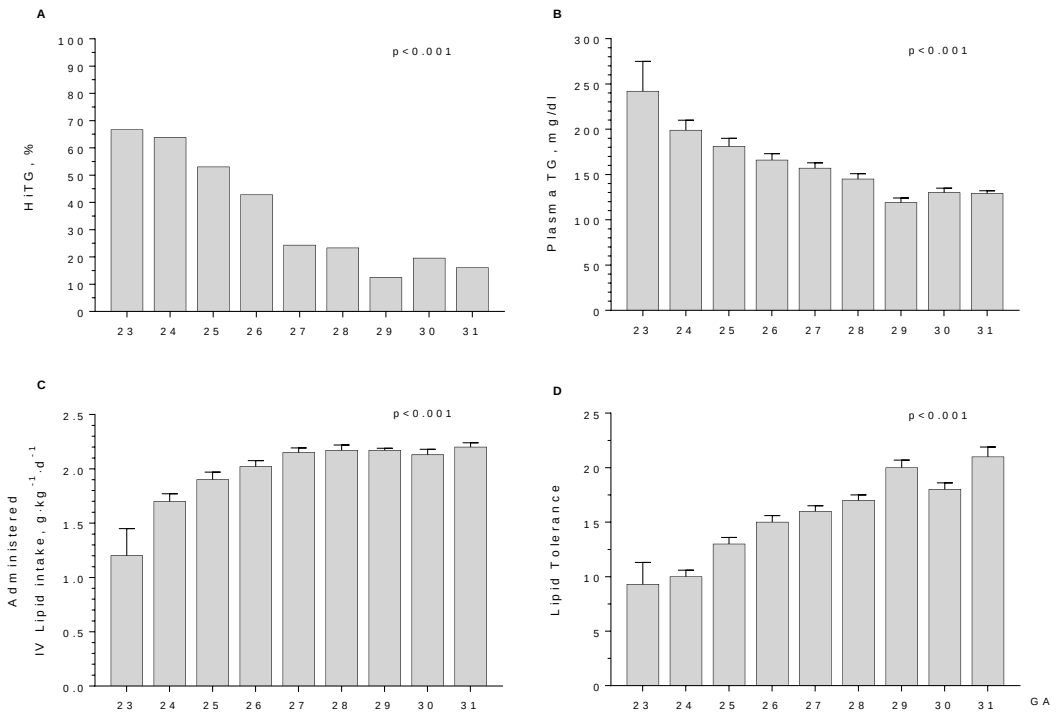


***Figure 1****. Incidence of HiTG (A), plasma TG concentration (B), administered IV lipid intake (C) and LT (D) among GA weeks ($23^{0/7}$–$23^{6/7}$, n=12; $24^{0/7}$–$24^{6/7}$, n=47; $25^{0/7}$–$25^{6/7}$, n=49; $26^{0/7}$–$26^{6/7}$, n=104; $27^{0/7}$–$27^{6/7}$, n=115; $28^{0/7}$–$28^{6/7}$, n=106; $29^{0/7}$–$29^{6/7}$, n=80; $30^{0/7}$–$30^{6/7}$, n=102; $31^{0/7}$–$31^{6/7}$, n=57). Data were presented as mean±SE or percentage. One-way ANOVA or Chi-Square test were used for the analysis. P-value<0.05 was considered significant. LT was calculated as the ratio of intravenous lipid intake ($g \cdot kg^{-1}$) preceding sampling to plasma triglycerides ($g \cdot dL^{-1}$). Administered IV lipid intake was calculated as the mean administered intake from DOL 4 to 7. GA: gestational age; HiTG: hypertriglyceridemia; IV: intravenous; TG: triglyceride.*

***Risk factors for HiTG:*** Perinatal variables associated with HiTG at univariate analysis were GA, $SGA^{10th\ centile}$, exposure to antenatal steroids, administered IV lipid intake, fish oil containing lipid emulsions (FO LEs), IV AA intake, DOLs,

HIP, RDS, PDA, IVH III-IV, asphyxia and Apgar at 5 minutes (Pearson correlation, $p<0.1$). Logistic regression analysis showed that $SGA^{10th\ centile}$, IVH grade III and IV, PDA and IV lipid intake were risk factors for HiTG, whereas older GA, IV AA intake and the use of FO LEs were protective (**Table 1**). The risk of HiTG was about twice as high in infants diagnosed with IVH grade III and IV, PDA and SGA and it was reduced by 12% for each additional week of gestation and by 19% for each extra grams of IV AA. HiTG risk was increased by about 200% for each additional gram of IV lipid intake while the use of IV FO LEs reduced the risk of HiTG by about 40%.

**Table 1**. Multiple logistic regression model to predict risk of HiTG.

| **Independent factors** | **Exp(B) (95% C.I.)** | **p-value** |
|---|---|---|
| GA (weeks) | 0.88 ( 0.85 - 0.92 ) | 0.000 |
| Apgar at 5 minutes | 1.03 ( 0.92 - 1.15 ) | 0.590 |
| Antenatal steroids | 0.98 ( 0.62 - 1.55 ) | 0.916 |
| HIP | 0.50 ( 0.17 - 1.41 ) | 0.189 |
| IV Lipid Intake (g·kg-1d-1) | 1.96 ( 1.59 - 2.4 ) | 0.000 |
| FO LEs | 0.62 ( 0.46 - 0.84 ) | 0.002 |
| IV AA intake | 0.81 ( 0.66 - 0.98 ) | 0.034 |
| DOLs | 1.04 ( 0.97 - 1.12 ) | 0.217 |
| SGA10th centile | 1.94 ( 1.43 - 2.65 ) | 0.000 |
| Asphyxia | 1.83 ( 0.93 - 3.6 ) | 0.078 |
| IVH grade III and IV | 1.80 ( 1.07 - 3.05 ) | 0.028 |
| PDA | 1.36 ( 1.01 - 1.82 ) | 0.042 |

| | | |
|---|---|---|
| RDS | 1.19 ( 0.89 - 1.6 ) | 0.238 |

*P-value<0.05 was considered significant. AA: amino acid; GA: gestational age; DOLs: days of life; FO LEs: fish oil lipid emulsions; HIP: Hypertension in pregnancy; HiTG: hypertriglyceridemia; IV: intravenous; IVH: intraventricular haemorrhage; SGA: small-for-gestational-age; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome.* $R^2$*= 0.6, p<0.001 (no. of samples: 1812)*

***The association between LT and clinical data:*** Pearson's correlation analysis indicated that LT was associated with GA, $SGA^{10th\ centile}$, exposure to antenatal steroids, FO LEs, DOLs, Apgar at 5 minutes, IV AA intakes, IV glucose intakes, RDS, asphyxia, PDA, LOS and IVH III-IV (Pearson correlation, p<0.1).
Multiple linear regression analysis showed that older GA, the use of FO LEs and the IV AA and glucose intakes were positively associated with LT. $SGA^{10th\ centile}$, PDA, RDS, IVH III-IV and LOS were negatively associated with LT (**Table 2**).

**Table 2**. Multiple linear regression model to predict LT.

| **Independent factors** | **B (95% C.I.)** | **p-value** |
|---|---|---|
| GA (weeks) | 0.24 ( 0.11 - 0.37 ) | 0.000 |
| Apgar at 5 minutes | 0.16 ( -0.19 - 0.52 ) | 0.369 |
| Antenatal steroids | 1.05 ( -0.44 - 2.54 ) | 0.166 |

| | | |
|---|---|---|
| FO LEs | 1.89 ( 1.00 - 2.78 ) | 0.000 |
| IV AA intake(g·kg-1·d-1) | 1.18 ( 0.48 - 1.88 ) | 0.001 |
| IV glucose intake(g·kg-1·d-1) | 0.61 ( 0.39 - 0.82 ) | 0.000 |
| DOLs | 0.07 ( -0.13 - 0.28 ) | 0.486 |
| RDS | -1.14 ( -2.02 - -0.26 ) | 0.011 |
| PDA | -1.73 ( -2.68 - -0.78 ) | 0.000 |
| Asphyxia | -2.28 ( -4.87 - 0.31 ) | 0.084 |
| SGA10th centile | -2.96 ( -3.94 - -1.90 ) | 0.000 |
| IVH grade III and IV | -3.96 ( -5.90 - -2.02) | 0.000 |
| LOS | -8.56 ( -16.70 - -0.42 ) | 0.039 |

*P-value<0.05 was considered significant. AA: amino acid; DOLs: days of life; FO LEs: fish oil lipid emulsions; GA: gestational age; IV: intravenous; IVH: intraventricular haemorrhage; LOS: late onset sepsis; SGA: small-for-gestational-age; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome. $R^2$=0.8, p<0.001 (no. of samples: 1767)*

## DISCUSSION

We studied HiTG in 672 preterm infants on routine PN from birth who were treated according to the same clinical guidelines and nutrition protocol over a 14 years' period.

Next to the incidence of HiTG we calculated, in all our patients, LT. In our unit where a tight lipid monitoring policy is effective in keeping plasma TG below the maximum threshold value of 250 $mg \cdot dL^{-1}$, we believe that LT could be used as a reliable index of the IV lipid metabolizing capacity of a subject during PN. In addition, while HiTG is a dichotomous variable, LT offer the advantages of a continuous variable.

We would like to comment the following findings.

Our study patients received markedly lower lipid intakes than the recommended target values of current guidelines. Seventy per cent of HiTG episodes occurred at IV lipid intake of less than 2.5 $g \cdot kg^{-1} \cdot d^{-1}$ and less than 25% of our patients were able to receive more than 3 $g \cdot kg^{-1} \cdot d^{-1}$ without developing HiTG. Our data is in line with other reports [6, 10], that also show that lipid clearance is often impaired in very preterm infants.

We wonder if a more moderate IV lipid intake for these infants could avoid repeated blood sampling for lipid titration. On the other hand, additional studies are needed to clarify the optimal strategy for lipid titration both in terms of target lipid intakes and of plasma TG threshold values. We recently published a case-control study comparing the clinical outcome of 136 pairs of preterm infants with and without HiTG [13], and surprisingly, we found no differences neither in the major complication of prematurity nor in anthropometry and neurodevelopment at 2 years of corrected age. These findings were quite reassuring to us and this information may prompt new study exploring the safety of higher threshold values.

We found that the incidence of HiTG was markedly higher in preterm infants below 28 weeks' gestation and in SGA infants. This information is in line with previous reports [1, 5, 10-12, 15] and it can be explained by the low lipoprotein lipase activity [6, 16] and/or worse endothelial function associated with prematurity and SGA status [17, 18].

In this paper we studied LT as the ratio of intravenous lipid intake ($mg \cdot kg^{-1}d^{-1}$) preceding sampling to plasma triglycerides ($g \cdot dL^{-1}$). Please note that, a low efficiency of TG metabolism can occur even in case of plasma TG concentration within the normal ranges (i.e. 200 $mg \cdot dL^{-1}$) with a low IV lipid intake (1.0 $g \cdot kg^{-1} \cdot d^{-1}$). Conversely, with high IV lipid intake (i.e. 2.5 $g \cdot kg^{-1} \cdot d^{-1}$) LT can be in the high range if plasma TG concentration is low (i.e.80 $mg \cdot dL^{-1}$).

Because of the continuous nature of this variable throughout the whole range of lipid intake and across all plasma TG values we are presently studying if LT could be a useful marker for lipid clearance and ultimately could prevent HiTG.

Using a multiple approach, we found a significant association of both HiTG and LT with several of the major complications of prematurity.

We also found a significant association between LT and both AA and glucose intakes. We do not have a clear explanation for this finding, and we could not find any published data on the interaction between IV AA and glucose intake with LT. We wonder if this association may occur in somewhat healthier babies or if higher glucose and AA intake could be capable of stimulating insulin production which in turn can stimulate lipoprotein lipase and improve LT [19, 20]. In our view, the magnitude of this difference is, however, biologically small.

Of interest, the use of FO LEs was significantly associated with markedly and significantly lower incidence of HiTG and a higher LT. The effect of down-regulation of lipogenesis by FO LEs is well known in humans and it has also been reported by others and by our group in preterm infants on PN [21-24].

This study has some limitations. It is a retrospective study and it carries an inherent risk of biases. However, all data were prospectively recorded according to predefined criteria and nutrition protocols were unchanged during the study period. LT could not be calculated in case of nil IV lipid intake, but this occurred only in 3 patients.

In conclusion, in our large study cohort of 672 preterm infants on routine PN and with a strict TG monitoring, the IV lipid intakes were markedly lower than the target values recommended by ESPGHAN and ASPEN guidelines. LT was markedly reduced especially in preterm infants born between $23^{0/7}$ and $27^{6/7}$ weeks' gestation and in association with some of the major complication of prematurity. We believe that recommendations targeted to GA subgroups should be considered. The cost-benefit ratio of higher thresholds for plasma TG during PN remains to be studied.

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