Lipid, lipoprotein profile and hemorheology in preterm and full-term newborns: where is the difference?

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ABSTRACT

Aims The plasma lipids on the blood rheological characteristics have been studied by several authors and it has been proved that these repercussions have influence on fetal growth during pregnancy. Moreover, the blood rheology may generate the response of the newborn to certain physiological and pathological situations, neonatal polycythemia being the most studied rheological characteristic during the last years. Our aim was to analyze and compare lipid, lipoproteic profile and hemorheological characteristics in newborns.

Methods Fifty-four newborns were studied. They were divided into two groups according to the gestational age: group I consisted of 26 newborns (gestational age under 37 weeks) and Group II consisted of 28 newborns (gestational age over 37 weeks). The blood samples were collected by venepuncture between the first and third hour of life. We analyzed serum lipids, plasma viscosity and rate of red blood cell (RBC) rigidity.

Results The plasma viscosity is similar in the full-term and preterm newborns, however, rigidity rate (RR) is significantly higher in preterm newborns. The gestational age of the newborns was related to triglycerides (TG), free fatty acids (FFA) and high-density lipoprotein cholesterol (HDL). Preterm newborns showed lower plasma concentrations of TG, phospholipids (PhL) and HDL. However, the levels of low-density cholesterol (LDL), FFA/TG and LDL/HDL ratio were significantly higher in the newborns with lower gestational age.

Conclusions Although more thorough clinical assays are necessary, we observed that preterm newborns should have a LDL concentration and a LDL/HDL ratio higher than term newborns.

INTRODUCTION

Although lipid and lipoprotein concentrations in adults can be determined by ethnic[1], nutritional[2], hereditary[3], or physiological[4] characteristics, newborn show a lipid concentration dependent on vascularization and metabolism of placenta[5,6], materno–placental transference of nutrients and fetal maturity[7]. The repercussions of plasma lipids on rheological characteristics have been studied by several authors[8,9], the repercussions of blood rheology on fetal growth during the pregnancy having been confirmed[10,11]. Moreover, blood rheology may generate the newborn's response with regard to certain physiological and pathological situations, neonatal polycythemia being the most studied rheological characteristic in the last few years[12–15].

Gestational age of the newborn and their concentration of plasma lipids in relation to blood rheology have not been thoroughly studied. Some studies show rheological differences between preterm and full-term newborns, these being related to different protein compositions of the plasma[16], different morphology of red blood cells (RBC)[17,18], or different production of RBC due to the erythropoietin[19,20]. The rigidity rate of RBC depends on three fundamental factors: cellular geometry (relationship area/volume)[21],

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intraerythrocyte viscosity and physical properties of the membrane[22,23]. On the other hand, hematrocrit is another important characteristic which we take into account when analyzing blood rheology in newborns, as it is going to change progressively with the gestational age[24]. Our aim is to analyze and compare the lipidic, lipoproteic and hemorheological characteristics of plasma in newborns.

MATERIALS AND METHODS

Samples from 54 newborns were obtained in our hospital. All cases of each group were selected in chronological order with regard to birth, both full-term newborns and preterm newborns, those newborns that had a therapeutic intervention before the third hour of life were excluded from our studies. None of the newborns in Group I showed pathological manifestations during the neonatal period. This project was approved by the Hospital Ethical Committee and consent of parent or guardian was obtained in each case.

The samples were collected by venepuncture between the first and third hours of life – before the perfusion of parenteral fluids. In all cases, 2 ml of blood were collected and were divided into two volumes, one volume was transferred to a dry glass test tube containing 10 µl/ml 10% ethylenediaminetetraacetic acid (EDTA) for rheological determinations[16,25] and the other volume was kept in reserve for analytical determinations in serum. The samples were centrifuged at 2000 *g* for 30 min and the plasma and serum were separated from the cellular packet.

RBC count, cell volume and hemoglobin concentration were determined with a Coulter Counter (Coulter Electronics, Herts, UK). Low-density lipoprotein cholesterol (LDL) was calculated as the difference between the mass of cholesterol in the infranatant and high-density lipoprotein cholesterol (HDL)[26]. Enzymatic colorimetric methods were used for determination of cholesterol and triglycerides from all serum and lipoprotein lipids using commercial kits (Monotest Cholesterol (TC) and Triglyceride GPO-PAP; Boehringer, Mannheim, Germany) with an automated instrument (Kone Specific Clinical Analyzer, Kone, Espoo, Finland). The variation coefficient from the analysis of total cholesterol was 1.43 to 1.87 (+ 3 SD) and the one resulting from the HDL and triglyceride (TG) analysis was 2.13 (+ 1 SD). Free fatty acids (FFA; enzymatic microtechnique, Wako Chemicals Gmbh, Germany), phospholipids (PhL; enzymatic microtechnique, BioMerieux)[27]. Determination of apolipoprotein A-I (ApoA-I) and ApoB were based on immunoprecipitation measurement, enhanced by polyethyleneglycol at 340 nm[28]. The Kone Specific Clinical Analyzer and ApoA-I and ApoB reagents from Orion Diagnostica (Espoo, Finland) were used in the analyses.

Plasma viscosity was measured at 37 °C over the following 8 h as recommended by the International Committee for Standardization in Hemorheology, with a Harkness 8052 series capillary viscosimeter (Coulter Electronics)[29]. In accordance with the International Committee for Standardization in Hemorheology[30], a suspension of RBC 8% was obtained. After washing the cellular packet three times with the same volume of saline solution and a phosphate buffer (pH 7.4; osmolality 295 mOsm/kg), the filtration was performed within the 3 h after extraction. We used the method described by Schmid-Schönbein and colleagues[25]. We used a constant pressure of −10 cmH_2O and polycarbonate filters of 25 mm with 5 µm of mean pore diameter (Millipore). The passage time of 1 ml of phosphate buffer at 25 °C and then the passage time of a suspension of RBC 8% (T_s) were measured. For each sample two measurements were performed using different filters and we recorded the mean value of both measurements of each case. The filtrability was estimated by rigidity rate (RR)[31]:

$$RR = \frac{T_s - T_p}{T_p \times \mathrm{Hto}} \times 100$$

where T_p is the passage time of the standard solution phosphate buffer, T_s is the passage time of the RBC suspension and Hto is the hematocrit.

The low shear whole blood viscosity (LSWBV) was calculated as follows[32]:

$$LnLSWBV = -0.606 + 0.0384 \times \mathrm{Hto};$$
$$LSWBV = e^{-0.606 + 0.0384 \times \mathrm{Hto}}$$

The high shear whole blood viscosity (HSWBV) was calculated on the basis of the following expression[24]:

$$LnHSWBV = 0.0047 + 0.0127 \times \mathrm{Hto};$$
$$HSWBV = e^{0.0047 + 0.0127 \times \mathrm{Hto}}$$

The data were analyzed statistically using Shapiro and Wilk's test, correlation and regression studies (Pearson's 'r'), and comparison of the means (*t* test).

RESULTS

We studied 54 newborns and they were divided into two groups according to the gestational age: Group I consisted of 28 newborns with a gestational age under 37 weeks [mean 32 weeks (SD 3)] and a mean weight of 1900 g (SD 680) and Group II consisted of 26 newborns with a gestational age equal to or over 37 weeks [mean 40 weeks (SD 1)] and a mean weight of 3500 g (SD 460). The gestational age was significantly related to TG concentration ($r = 0.63$; $p < 0.01$; 95% CI 0.44–0.77); however, we did not observe significant relations between gestational age and TC concentration. Gestational age was inversely related to LDL ($r = 0.55$; $p < 0.001$; 95% CI −0.33 to −0.75) and LDL/HDL ($r = -0.56$; $p < 0.01$; 95% CI −0.34 to −0.71) and FFA/TG ratios ($r = -0.48$; $p < 0.01$; 95% CI −0.24 to −0.66). On the other hand, gestational age was not significantly related to plasma viscosity of newborns, or to high shear whole blood viscosities (HSWBV) and low shear whole blood viscosity (LSWBV).

In Table 1 the rigidity rate is significantly higher in the preterm newborns. The plasma viscosity, and the blood viscosity for high and low shear were calculated on the basis of the equation of Welch and colleagues[24] and significant differences between preterm and full-term newborns were not found. Preterm newborns showed lower plasma concentrations of TG, phospholipids (PhL), FFA, HDL, ApoA and ApoB as shown in Table 2. However, LDL concentrations are significantly higher in newborns with low gestational age. The study of the lipoprotein ratios showed significant differences among LDL/HDL, HDL/ApoA and FFA/TG ratios (Table 2).

Table 1 Hematological and hemorheological values in term and preterm newborns

	Term newborn	Preterm newborn
RBC (10^6/l)	4.7 (0 64)	4.3 (0 44)*
Hemoglobin (g/dl)	16 8 (2.44)	15.8 (1 75)
Hematocrit (%)	49.4 (6.79)	47.7 (5.52)
MCV (fl)	105 6 (4 84)	110.4 (7 45)***
MCH (pg)	36 4 (1 92)	36 3 (2.63)
MCHC (g/dl)	34.2 (1 64)	33.5 (1.76)
Plasma viscosity (mPa.s)	0.95 (0.12)	0 90 (0 09)
Buffer phosphate filterability (s)	1.10 (0.17)	1 08 (0.17)
RBC suspension filterability (s)	3.51 (1.27)	4.14 (1.61)
Rigidity rate	26 7 (11.8)	35.07 (15 9)*
High shear whole blood viscosity (mPa.s)	1 88 (1 09)	1.84 (1.07)
Low shear whole blood viscosity (mPa s)	3 64 (1.29)	3.41 (1 02)
pH	7 35 (0.06)	7.29 (0.12)
pCO_2mmHg	52 35 (24.8)	71.1 (37 6)*
pO_2mmHg	37 05 (4 53)	38.03 (9 11)

RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; *$p < 0.05$, ***$p < 0.001$, statistical significance observed between groups

Table 2 Lipid and lipoprotein ratios in term and preterm newborns

	Term newborn	Preterm newborn
Cholesterol total (mmol/l)	2 05 (0 33)	1 99 (0 71)
Triglycerides (mmol/l)	1.42 (0 53)	0.72 (0 44)***
Phospholipids (g/l)	1.58 (0.35)	1 28 (0 30)***
Apolipoprotein A (g/l)	0.87 (0 11)	0 79 (0 12)*
Apolipoprotein B (g/l)	0 49 (0 07)	0.42 (0 08)**
HDL (mmol/l)	1.00 (0.27)	0 72 (0.43)*
LDL (mmol/l)	0 41 (0.30)	0 90 (0.48)***
FFA (mmol/l)	0.69 (0.17)	0 57 (0 22)*
ApoB/ApoA ratio	0.57 (0 09)	0 54 (0.14)
TC/HDL ratio	2.31 (0 60)	2.74 (0 69)***
LDL/HDL ratio	0.46 (0 40)	1 10 (0.77)***
HDL/ApoA ratio	1.24 (0.31)	0 98 (0.22)***
FFA/TG ratio	0.55 (0.35)	1.09 (0.59)***

HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FFA, free fatty acid. TC/HDL ratio, total cholesterol/high-density lipoprotein cholesterol ratio; LDL/HDL ratio, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio; HDL/ApoA ratio, high-density lipoprotein cholesterol/apolipoprotein A ratio; FFA/TG ratio, free fatty acid/triglycerides ratio *$p < 0.05$; **$p < 0.01$, ***$p < 0.001$, statistical significance observed between groups

DISCUSSION

Blood rheology in newborns

As in previous studies[16], we did not find significant differences between plasma viscosity in preterm and full-term newborns. Fibrinogen is the molecule that has higher influence on plasma viscosity[33,34], and its plasma concentration increases according to gestational age. From these observations, we can expect higher values of plasma viscosity in full-term than in preterm newborns[35,36]. However, the different fibrinolytical activity in the newborns, which depends on gestational age, or acute or hypoxia stress during delivery[16,37], could explain our values of plasma viscosity in both groups. Likewise, Linderkamp and colleagues[17], agree with us, since our results do not show significant differences between the passage time of RBC in full-term and preterm newborns. However, when performing an adjustment on the passage time of buffer and the suspension of hematocrit, we observe significant differences between the rigidity rate of full-term and preterm newborns. Even though several authors[38] think that the accumulation of RBC lactic acid may generate the increase of RBC rigidity, the lack of significant changes in the pO_2 and pH values in our study shows that factors other than RBC lactic acid have to be related to the variability of RBC rigidity rate. We, like Reinhart and co-workers[36], think that a higher volume of RBC in preterm newborns is a determinant characteristic of the different rigidity rates observed between full-term and preterm newborns. Previous studies[39] have shown higher values of blood viscosity in adults than in the newborns. These differences could be explained either by a difference in the plasma viscosity or by the influence of plasma lipidic profile on RBC membrane and on its rigidity[9]. Many of these premature newborns had already developed a respiratory distress together with a pCO_2 increase. It could be expected that an increase of pCO_2 such as that observed in the group of preterm newborns may cause acidosis, which could justify the increase of erythrocytary rigidity in the group. However, its pH values do not differ from those observed in the group of term newborns. This fact is surely due to the tampon effect of bicarbonate, i.e. a compensated respiratory acidosis is produced. In the absence of acidosis, pCO_2 increase does not seem to be the only cause of the erythrocytary rigidity increase observed in premature newborns.

Blood lipidic characteristics in newborns

As shown in Table 2, TG concentration in term newborns is significantly higher than in preterm newborns, in which a linear relation between gestational age and TG concentration in blood is observed. Bayes and colleagues[40] think that TG concentrations, both in the mother and in the fetus, do not have a linear relation, although TG concentration in maternal blood increases progressively during pregnancy without any evidence of different lipolysis of TG in the mother or in the newborn[41]. Bayes and colleagues[40] think that the activity of placental lipoprotein lipase and phosphorylase increase during acute stress or acidosis. On the other hand, lipidic hydrolysis of materno–placental space increases the FFA contribution in the fetus.

Regarding our findings, on the one had we cannot justify that hypoxic stress or lower pH are only responsible for a higher hydrolysis of TG in preterm newborns as we have not observed evident hypoxemia or acidosis in the group with a lower gestational age (Table 1). Bayes and co-workers[40] found a significantly higher TG concentration in those newborns with acute stress. On the other hand, our findings regarding the increase of atherogenic rates in the maternal plasma, which contribute to a decrease of placental blood flow with a lower fetal growth[41], could indicate that placental ischemia is the mechanism contributing to the progressive increase in the activity of placental lipoprotein lipase and phosphorylase. Our findings coincide with those of Lim and colleagues[42] as they found increased phospholipase A_2 concentrations in pregnancies with pre-eclampsia. Likewise, Endresen and co-workers[43] found an increase in lipolysis of endothelial cells *in vitro* which come from women with pre-eclampsia.

Therefore, observational data[44] suggest that full-term newborns show higher ApoA concentrations and lower HDL concentrations. There is a quantitative difference in the HDL composition since full-term newborns have lower ApoA concentrations than preterm newborns. Besides, HDL/ApoA ratio values in preterm newborns are similar to those in pregnant

women[43]. Lipidic changes in the fetus could be an evolutionary mechanism of adaptation to postnatal life where oxygen concentrations are higher, and so the risk caused by the lipid peroxidation is greater[44]. The peroxidative modifications of lipoproteins may intervene in the tissue damage[44] and in the transitory vasoconstriction due to lipidic peroxides[45]. On the basis of these findings, preterm newborns would be in a situation of high vulnerability with regard to oxidative stress due to circumstances such as higher LDL plasma concentrations. Although more thorough clinical assays are necessary, we observed that preterm newborns should have a higher LDL concentration and a higher LDL/HDL ratio than term newborns.

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