Effect of Preterm Birth on Postnatal Apolipoprotein and Adipocytokine Profiles

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Key Words

Prematurity · Apolipoproteins · Adipocytokines · Multiplex assay

Abstract

Background: Critical metabolic changes preparing for ex utero life may occur at the fetal age of approximately 28–32 weeks, and preterm birth <28 weeks postmenstrual age (PMA) may affect these pathways. Children born <28 weeks often have poorer outcomes possibly due to a major shift in metabolism, including nutritional supply and a shift in lipid-transporting particles and lipid profile. This shift may occur in apolipoprotein and adipocytokine levels, which may influence metabolism. **Objective:** To determine whether there is a shift in apolipoprotein and adipocytokine levels in neonates born at a gestational age (GA) of 28 and 32 weeks, respectively. **Methods:** Blood samples from 47 infants (GA 32 weeks, n = 30 and GA 28 weeks, n = 17) were collected at birth and, in the GA28 group, also at PMA 32 weeks. Apolipoproteins A-1, A-2, B, C-2, C-3, and E were analyzed, as well as adiponectin and leptin levels. **Results:** Serum levels of apolipoproteins A-1, C-2, C-3, and E were lower at birth in the GA28 group compared to the GA32 group. Adiponectin and leptin levels were low at birth in the GA28 group. In the GA28 group 4 weeks after birth, leptin levels were still low, whereas adiponectin levels had increased to levels similar to those found at birth in the GA32

group. Apolipoprotein A-1, C-2, C-3, and E levels were negatively correlated with days receiving total parenteral nutrition.

Conclusion: There are significant differences in apolipoprotein and adipocytokine levels, which can be associated with GA and birth weight. The impact of these changes on neonatal and future morbidity remains to be determined.

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Introduction

According to WHO, preterm birth is defined as birth before 37 completed gestational weeks and can be further subdivided into extremely preterm (<28 weeks), very preterm (28 to <32 weeks) and moderate or late preterm (32 to <37 weeks) [1]. There is a tremendous difference in risk associated with preterm birth depending on gestational age (GA) at birth, with a major shift occurring at about 28 weeks' postmenstrual age (PMA). Fatality risk is 28% when born at <28 weeks compared to 0.7% when born at 32–36 weeks. Also, morbidity rates are much higher when born at <28 weeks compared to those born at >32 weeks [2, 3]. This shift in morbidity and mortality at 28 weeks' PMA suggests a major shift of metabolic processes at around 28 weeks of gestation.

The third trimester is the period when many organs undergo the fastest growth and development rates, and there

is a pronounced increase in the relative amount of adipose tissue. At birth, there is a major shift in nutritional supply, with a transition from substrate flow from the placenta towards an adaption to a high-fat milk diet. This process requires a shift in the synthesis and metabolism of lipid-transporting particles, the composition of which changes from that before birth. An altered lipid profile has been shown in preterm infants compared to term infants [4–7].

As lipids are the main structural components and therefore affect growth and development, lipid metabolism is of major importance in neonatal nutrition. There are many components involved in the complex lipid metabolism and transport system. One key group is apolipoproteins. Apolipoprotein A-1 (Apo A-1) is the main protein component of high-density lipoprotein (HDL) in plasma and promotes fat efflux, including cholesterol, from tissues to the liver. Apo A-2 is the second most abundant protein component of HDL. Apo B is the primary apolipoprotein of low-density lipoprotein (LDL), which carries cholesterol to tissues. Apo C-2 is a component of very low LDL and activates the enzyme lipoprotein lipase as a cofactor, whereas Apo C-3 inhibits lipoprotein lipase activity [8]. In the central nervous system, Apo E is involved in the transport delivery and clearing of lipids in the brain via Apo E receptors [9]. Both leptin [10] and adiponectin [11] levels in cord blood are associated with the lipid profile in neonates.

Our hypothesis for this study was that critical metabolic changes preparing for ex utero life may occur at the fetal age of approximately 28–32 weeks. The aim of the present study was to investigate apolipoprotein and adipocytokine levels in neonates born at GA 28 or 32 weeks, respectively.

Patients and Methods

Ethical Considerations

The protocol was approved by the Regional Ethical Review Board in Gothenburg, and the study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all parents.

Study Participants and Sample Collection

A total of 47 infants born at GA 27 weeks + 0 days to 28 weeks + 6 days ($n = 17$) or 32 weeks + 0 days to 33 weeks + 6 days ($n = 30$) were included in the study, referred to as the GA28 group and the GA32 group, respectively. Clinical characteristics of the study population are presented in table 1. From all infants, one serum sample was collected within 24 h after birth. From the GA28 group, an additional blood sample was collected at PMA 32 weeks. All serum samples were collected in connection with ordinary blood sampling. Exclusion criteria for participation in the study were serious malfor-

Table 1. Clinical and nutritional data

Characteristics	GA28, at birth ($n = 17$)	GA32, at birth ($n = 30$)
Preeclampsia	6 (35) ¹	4 (14) ²
Antenatal steroids	16 (94)	26 (96) ³
Male gender	8 (47)	18 (60)
Multiple birth	5 (29)	2 (7)
Cesarean section	15 (88)	16 (53)
Apgar score 1 min	9 (5–9)	9 (5–10)
Apgar score 5 min	9 (7–10)	10 (7–10)
Apgar score 10 min	10 (7–10)	10 (9–10)
Total parenteral nutrition	17 (100)	1 (3)
Total parenteral nutrition, days (min–max)	5 (3–13)	0 (0–2)
IRDS	12 (71)	2 (7)
BPD	7 (41)	0
PDAop	1 (6)	0
NEC	1 (6)	0
Proliferative ROP	1 (6)	0
IVH	8 (47)	1 (3)

Data are presented as n (%) unless otherwise indicated. Apgar scores are presented as medians (min–max). IRDS = Infant respiratory distress syndrome. BPD = bronchopulmonary dysplasia; PDA = patent ductus arteriosus; NEC = necrotizing enterocolitis; ROP = retinopathy of prematurity; IVH = intraventricular hemorrhage.

¹ Missing data, $n = 1$. ² Missing data, $n = 2$. ³ Missing data, $n = 3$.

mations, treatment with medicines other than antibiotics and blood or plasma transfusion before the first blood sample – or <1 week before the second blood sample was collected from the GA28 group. Serum samples were stored at -70°C and not thawed until analysis.

Feeding Regimen

Enteral feeding with increasing amounts of breast milk was introduced early (2–48 h after birth). When full enteral feeding was not achieved, supplementary parenteral nutrition with amino acids and fat was given within the first days of life. For infants with a birth weight below 1,500 g the breast milk was fortified with 0.8 g protein/100 ml (gradually introduced over 1 week) from age 10 days until the infant weighed approximately 2 kg. When the mother's milk was insufficient, unpooled donors' milk was given.

Growth Measurement

Standardized weight measurements were performed on the same day as blood sampling. A standard deviation score (SDS) for weight ($\text{weight}_{\text{SDS}}$) was calculated from an intrauterine growth curve based on ultrasonically estimated fetal weights in Scandinavia [12]. Anthropometric data are shown in table 2.

Multiplex Apolipoprotein Assay

Serum samples were diluted 1:10,000 and Apo A-1, A-2, B, C-2, C-3, and E levels were analyzed with a human apolipoprotein 6-plex assay (Millipore Corporation, Billerica, Mass., USA) ac-

Table 2. Anthropometric data

Characteristics	GA28 (n = 17)	GA32 (n = 30)
Birth weight, g	1,005 (555–1,155)	1,982 (1,365–2,495)
Birth weight _{SDS}	–1.54 (–4.88 to –0.10)	–0.60 (–3.06 to 1.68)
Weight at PMA 32 weeks, g	1,495 (930–2,040)	
Weight at PMA 32 weeks, SDS	–2.16 (–4.91 to –0.98)	
Gain in height, g	540 (295–1,005)	
Gain in height, SDS	–0.45 (–1.27 to 0.49)	

Data are presented as medians (min–max).

Table 3. Serum levels of apolipoproteins and adipocytokines

	GA28, at birth (n = 17)	GA28, at 32 weeks PMA (n = 17)	p ₁	GA32, at birth (n = 30)	p ₂	p ₃
Apo A-1, µg/ml	670 (345–873)	1,353 (738–3,693)	<0.001	894 (563–1,139)	<0.001	<0.001
Apo A-2, µg/ml	166 (78–254)	303 (170–910)	<0.01	178 (128–273)	n.s.	<0.001
Apo B, µg/ml	16 (0–1021)	320 (0–1,383)	<0.01	8 (0–629)	n.s.	<0.001
Apo C-2, µg/ml	31 (7–77)	56 (32–161)	<0.001	56 (17–88)	<0.001	n.s.
Apo C-3, µg/ml	53 (6–153)	99 (63–238)	<0.001	134 (29–248)	<0.001	n.s.
Apo E, µg/ml	72 (20–170)	76 (38–188)	n.s.	96 (19–241)	<0.05	n.s.
Adiponectin, µg/ml	1.8 (0.6–14.1)	16.6 (4.3–77.3)	<0.001	22.5 (3.7–50.6)	<0.001	n.s.
Leptin, ng/ml	0.06 (0.00–1.00)	0.01 (0.00–2.40)	n.s.	0.63 (0.00–6.48)	<0.01	<0.01

Data are presented as medians (min–max). p₁: p value GA28 group at birth vs. GA28 group at PMA 32 weeks; p₂: p value GA28 group at birth vs. GA32 group at birth; p₃: p value GA28 group at PMA 32 weeks vs. GA32 group at birth. n.s. = Nonsignificant.

cording to the manufacturer's instructions. Samples were analyzed on a Bio-Plex 200 instrument (Bio-Rad Laboratories, Hercules, Calif., USA) with Bio-Plex Manager 6.1 software. Doublet discriminator gate settings were set at 4,335–10,000 in accordance with Bio-Plex Manager instructions.

ELISA Analyses

Leptin. Serum samples were diluted 1:5, and leptin levels were assayed with a human leptin ELISA kit (Mediagnost, Reutlingen, Germany). Intra-assay coefficients of variation (CVs) were 3.0% at 5.2 ng/ml and 4.1% at 13.8 ng/ml, and the interassay CV was 20.2% at 6.7 ng/ml. The functional sensitivity limit of the assay was 0.3 ng/ml.

Adiponectin. Serum samples were diluted 1:306, and adiponectin levels were assayed with a human adiponectin ELISA kit (Mediagnost). Intra-assay CVs were 3.8% at 3.9 µg/ml and 4.7% at 13.1 µg/ml, and the interassay CV was 16.3% at 9.9 µg/ml. For values >80 µg/ml, samples were further diluted with assay diluent, and the assay was repeated so that the results fell within the range.

Statistics

Basic data analyses on multiplex data were performed with Bio-Plex Data Pro software. Additional data analyses were performed with SPSS software version 20. All statistical analyses were per-

formed with nonparametric tests. Differences between independent groups were performed by the Mann-Whitney U test and between related groups by the Wilcoxon signed-rank test. Correlation analyses were performed by the Spearman rho test. The level of significance was set at $p < 0.05$.

Results

Apolipoprotein Serum Levels Measured by Multiplexing

Apo A-1, C-3, C-2, and E levels were lower at birth in the GA28 group compared to at birth in the GA32 group. In the GA28 group, Apo A-1, A-2, B, C-2, and C-3 levels increased from birth to postnatal age (PNA) 4 weeks (PMA 32 weeks). When apolipoprotein levels in serum collected from the GA28 group at PNA 4 weeks (PMA 32 weeks) were compared to levels at birth in the GA32 group, Apo A-1, A-2 and B levels were higher in the GA28 group. Detailed information on serum levels are presented in table 3.

Fig. 1. Serum levels of adiponectin (a) and leptin (b), as measured by ELISA. ** $p < 0.01$; *** $p < 0.001$.

Fig. 2. Correlation between weight and serum levels of adiponectin (a) and leptin (b), as measured by ELISA. ** $p < 0.01$; *** $p < 0.001$.

Serum Levels of Adipocytokines

Adiponectin. Serum levels of adiponectin at birth were lower in the GA28 group compared to at birth in the GA32 group. At PNA 4 weeks (PMA 32 weeks) in the GA28 group, levels increased similar to those found at birth in the GA32 group (fig. 1a; table 3). There was a positive correlation between weight and adiponectin levels ($r = 0.692$, $p < 0.001$; fig. 2a).

Leptin. In the GA28 group, serum levels of leptin were significantly lower, both at birth and at PNA 4 weeks

(PMA 32 weeks), compared to levels at birth in the GA32 group (fig. 1b; table 3). Leptin levels were nonlinearly correlated with weight ($r = 0.617$, $p < 0.001$). However, leptin levels exceeding 1 ng/l could not be detected in any child weighing <1,900 g (fig. 2b).

Growth and Parenteral Nutrition in Relation to Apolipoprotein and Adipocytokine Levels

Weight at birth for both groups and at PMA 32 weeks in the GA28 group are presented in table 2. In summary,

Table 4. GA28 group: growth and parental nutrition in relation to weight, apolipoprotein and adipocytokine levels

	At birth, r	At PMA 32 weeks, r	Change from birth to 32 week's PMA, r
<i>Gain in weight</i>			
Total parental nutrition	-0.46	-0.46	
Apo A-1	-0.07	0.35	0.22
Apo A-2	-0.14	0.28	0.34
Apo B	-0.37	0.29	0.58*
Apo C-2	0.54*	0.05	-0.23
Apo C-3	0.43	0.32	-0.08
Apo E	0.37	-0.35	-0.33
Leptin	-0.67**	0.39	0.58*
Adiponectin	0.49	0.28	0.14
<i>Parental nutrition</i>			
Weight	-0.11	-0.30	-0.46
Weight _{SDS}	-0.28	-0.31	0.10
Apo A-1	-0.55*	0.01	0.27
Apo A-2	-0.45	0.13	0.28
Apo B	-0.33	0.02	0.13
Apo C-2	-0.75***	-0.21	-0.23
Apo C-3	-0.72***	-0.18	-0.53*
Apo E	-0.70**	0.12	0.39
Leptin	0.15	-0.37	-0.40
Adiponectin	-0.31	-0.13	-0.17

* $p < 0.05$; ** $p < 0.01$; *** $p \leq 0.001$.

infants in the GA28 group were born at lower weights than infants in the GA32 group – birth weight ($p < 0.001$) and birth weight_{SDS} ($p < 0.01$). Weight gain in grams and duration of total parenteral nutrition in relation to apolipoprotein and adipocytokine levels in the GA28 group are presented in table 4. There were no correlations with weight gain in SDS.

Discussion

In summary, this study found lower levels of most apolipoproteins as well as adiponectin and leptin at birth in very preterm infants than in moderately preterm infants. In very preterm infants, adiponectin levels increased 4 weeks after birth, whereas leptin levels remained low. Leptin levels were undetectable or very low in all infants weighing $<1,900$ g, independent of GA at birth.

Lipid metabolism has an important role in fetal development during the last stages of gestation. During fetal life,

the main nutritional sources are glycogen and fat, which are supplied by a substrate flow from the placenta to the fetus. At birth, adaption to a high-fat milk diet involves shifts in the synthesis, metabolism and composition of lipid-transporting particles [13]. The main energy sources during this period are fatty acids and ketone bodies. Fatty acids needed locally are provided by circulating lipids that contain a high proportion of apolipoproteins. Apolipoproteins control the cellular uptake of lipoproteins and work as lipid transport proteins and coenzymes. Synthesis of apolipoproteins is controlled by several factors, including dietary composition and hormones like insulin, glucagon and sex steroids. Thus, the expression of apolipoproteins is regulated by several hormones and pathways affected by preterm birth. In the present study, we found lower circulating levels of Apo A-1, C-2, C-3, and E in infants with a GA <29 weeks than in infants with a GA around 32 weeks. During pregnancy, intact lipid transfer across the placenta is crucial to secure a sufficient supply of essential fatty acids to the fetus. The placental transfer of fatty acids is increased during the second half of pregnancy in association with rapid fetal fat deposition [13].

In infants born very preterm, lipid metabolism might not be adapted to extrauterine life, with a consequent dysfunctional supply of essential fatty acids to different tissues [14]. A marked increase in very low LDL, HDL, and LDL triglycerides has been reported in cord blood around GA 32–34 weeks [6]. Some data support a neuroprotective role for Apo E [15, 16], whereas others found no relation between Apo E genotypes and neurodevelopmental outcome in preterm infants [17, 18]. In this study, the levels of Apo E at birth in infants born at GA 28 weeks were still low 4 weeks after birth, which is interesting in the light of the high risk of neurocognitive impairment associated with prematurity [2, 17, 18].

In line with our results, a positive correlation between Apo A-1 levels in cord blood and GA has been reported [19] – from 519 $\mu\text{g/ml}$ at GA 21–26 weeks to 869 $\mu\text{g/ml}$ at GA 33–36 weeks before a plateau was reached until GA 41–43 weeks. Lane and McConathy [4] found that in cord blood, Apo A-2, C-2 and E levels were inversely correlated with GA, whereas Apo D was positively associated with GA. One reason for partially inconsistent results compared to our study could be group classification, since older preterm study groups were included in previous papers [4, 5].

In the GA28 group, we found a strong negative correlation between duration of total parenteral nutrition received and Apo A-1, C-2, C-3, and E levels at birth. As these apolipoproteins were low in infants born at GA

<29 weeks we can speculate that low apolipoprotein levels at birth might reflect a more immature gut, even though gene expression was not investigated in this study. Positive effects on the HDL pattern after early enteral nutrition have previously been shown, and early enteral feeding facilitated a postnatal rise in Apo A-1, probably reflecting positive effects on gut maturation [20].

In humans, leptin plays a central role in maintaining the energy balance and regulation of energy homeostasis. Associations between leptin and lipid levels [21], as well as with factors involved in cholesterol metabolism [22], have been shown. However, the causal relationship between leptin and lipid metabolism has yet to be explained. Adiponectin has been implicated in the pathophysiology of insulin-mediated lipoprotein metabolism [23], and some studies [11], but not all [10], have shown an inverse correlation between adiponectin levels and LDL cholesterol in cord blood.

In line with our results, low fetal levels of leptin in preterm neonates have been reported – median 0.6 ng/ml until GA 34 weeks, and then a gradual increase to 3.5 ng/ml at full term. However, the range was high [24]. In this study, there was a positive correlation between leptin levels and birth weight in infants born at GA 32 weeks but not in those born <GA 29 weeks (data not shown). Change in leptin levels correlated positively with weight gain in grams, probably reflecting increased amounts of adipose tissue. Increasing adiponectin levels in cord blood, from GA 20 weeks to full term, have previously been shown – approximately 5 µg/ml at GA 28 weeks and 15 µg/ml at GA 32 weeks [25]. In our study, adiponectin levels did not correlate with birth weight in either of the GA groups. Our data suggest that adiponectin levels start to increase shortly after birth. In contrast, leptin levels were still low at 4 weeks after birth in the GA28 group. Our data suggest that a weight above approximately 1,900 g is needed to observe increased leptin levels. This is in line with previous data suggesting that a relationship between leptin and body fat mass develops early in life [26], whereas the adiponectin system might be more related to GA [25].

The clinical significance of our findings with respect to the preterm infant's adaption to extrauterine life has to be further elucidated. In addition to the suggested role in gut maturity, there are links between apolipoproteins, adipocytokines and thermogenesis. In mice 4–5 days old, leptin reduced temperature loss after starvation [27], and in a genetic atherosclerotic mouse model adiponectin rescued Apo E-deficient mice from cold-induced lipolysis with elevated LDL levels. In contrast, no cold-induced effects on lipolysis and LDL levels were observed in Apo E-intact mice [28].

The lack of a control group born full term is a limitation of this study. However, the main purpose of the study was to compare circulating levels of selected factors between GA 28 and GA 32 weeks, a period in which important metabolic maturations preparing for ex utero life might occur. Being born <GA 28 weeks or >GA 32 weeks is in most countries in the developed world associated with a major difference in morbidity risk. Another limitation is that the GA32 group, due to discharge, was not followed up with a blood sample 4 weeks after birth. Thus, conclusions regarding postnatal changes in different preterm groups cannot be drawn.

From the present study, we conclude that there are significant differences at birth in circulating levels of apolipoproteins and adipocytokines between very preterm and moderately preterm infants. The impact of these findings has to be further elucidated in a larger cohort, where biochemical data and long-term morbidity is followed longitudinally and related to the lipid metabolism.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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