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Factors Affecting the Lipid and Apolipoprotein Levels of Cord Sera

DANIEL M. LANE AND WALTER J. MCCONATHY[30]

Presbyterian Hospital and Laboratory of Lipid and Lipoprotein Studies, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA

Summary

In studying the human lipid transport system as it changes from the fetal to the adult form, data were collected on cord sera levels of lipids and apolipoproteins (A-I, A-II, ApoB, C-I, C-II, C-III, ApoD, and ApoE) from infants whose lipid metabolism might have been modified by a variety of factors present before, at, or after delivery. The results clearly indicated that many factors affect the levels of both lipids and apolipoproteins at birth. Method of delivery had little effect except in relation to either fetal immaturity (increased total cholesterol) or fetal stress (increased triglycerides). Birth weight was related to changes in free cholesterol, C-I, C-III, and ApoE levels. Gestational age had greater impact upon both serum lipids and apolipoproteins. With increasing fetal maturity, total cholesterol, free cholesterol, A-II, C-II, and ApoE progressively fell whereas triglyceride and ApoD rose.

A variety of clinical disorders were also associated with changes in serum lipid and apolipoproteins. Anencephaly produced marked increases in both free and total cholesterol as well as most apolipoproteins. Significant reductions in triglyceride and ApoD levels were found in infants who subsequently became ill in the postnatal period with problems relating to carbohydrate metabolism (*e.g.*, infants of diabetic mothers). Infants with respiratory distress were found to have decreased levels of total cholesterol and ApoB, both of which are increased in prematurity, a condition with which respiratory distress (RD) is usually associated. The changes in cord sera lipid and apolipoprotein levels found in a variety of clinical situations may provide new diagnostic approaches to postnatal problems arising in the newborn.

Abbreviations

AGA, appropriate for age
C-section, Caesarean section
LGA, large for gestational age
LTS, lipid transport system
RD, respiratory distress
SGA, small for gestational age
TC, total cholesterol

Earlier reports (1, 12, 14, 16, 24, 27) have shown an association between perinatal conditions and levels of cord serum lipids. The majority of these studies have shown that lipid levels are altered under conditions related to perinatal distress (1, 12, 27). The purpose of the present study was to extend these observations to a wider variety of perinatal conditions as a basis for determining which factors, either maternal or fetal in origin, affect various components of the fetal plasma lipid transport system (LTS).

Previously, data on cord sera lipids and apolipoproteins of infants whose weight and gestational ages were normal and who had been delivered vaginally without complication have been presented (20). Levels of the serum lipids and apolipoproteins were found to be lower than those of adult sera except for C-I, C-II, and ApoE, all of which approached adult levels. This report is an extension of our previous study and includes data from a large group of infants with a variety of clinical conditions that might produce changes in serum lipids or apolipoproteins at birth. Conditions evaluated for their effects on the cord serum LTS included: weight, weight and gestational age, mode of delivery, congenital anomalies, and a variety of perinatal disorders. Attempts were made to describe those factors that have significant effects upon levels of cord serum lipids and apolipoproteins.

MATERIALS AND METHODS

This study was started in early 1976 and lasted approximately 3½ years, during which 4618 cord sera samples were collected. From those, individual analyses were performed on 2043 samples, of which 1716 had been collected consecutively. The surplus sera obtained was pooled for more extensive evaluation of specific components. As the study progressed, emphasis was placed on collection from infants who were not normal, and on pooling of samples from normal infants, thereby introducing bias toward the abnormal for the total population.

For the purposes of this study, cord sera measurements were made on a group of newborns who were subsequently separated into several study groups, depending upon clinical findings at or shortly after birth (Table 1). The first group included a comparison of a total population with the method of delivery. Infants delivered vaginally were separated into normal (cephalic presentation, birth weight 2.5–4.0 kg, gestational age 39–41 wk) and breech presentation. Infants delivered by Caesarean section (C-section) were subdivided into 3 groups: initial, repeat, and breech presentation.

The second group was separated by birth weight into the following categories: >4.0 kg, 2.5–4.0 kg, 2.0 to <2.5 kg, 1.5 to <2.0 kg, and <1.5 kg. A third group studied was comprised of low (<2.5 kg) and high (>4.0 kg) birth weight infants differing in gestational age. The small infants were divided into those <37 wk (appropriate for gestational age, AGA) and those >37 wk (small for gestational age, SGA) gestation, whereas the large infants were divided into those <42 wk (large for gestational age, LGA) and those ≥42 wk (AGA) gestation as suggested by Bernard *et al.* (5).

Another group of infants was characterized by the presence of a variety of congenital variants, some of which were not abnormal. Diagnosis included twins (all types), anomalous male genitalia (hydrocele or undescended testis), supernumerary digits, anencephaly, cleft palate, and Down's syndrome. The last group was composed of infants who developed problems either at or shortly after birth. Levels were evaluated in disorders associated with increased serum bilirubin, respiratory distress, and defects of carbohydrate metabolism.

The determination of both physical and clinical criteria was made by a variety of health professionals. Birth weight was determined upon admission to the Newborn Nursery at Presbyterian Hospital by nursery personnel. Gestational age was estimated by the delivering physicians (members of the Departments of Obstetrics-Gynecology or Family Medicine) based upon prenatal exams and estimated dates of conception. The method of

Table 1. *Criteria for various study groups*

Delivery mode group
1. Population (all infants)
2. Normal infants (2.5–4.0 kg; 39–41 wk gestation; vaginal delivery; no major complications)
3. Caesarean section: initial, repeat, or breech presentation
4. Vaginal breech delivery

Weight groups
1. >4.0 kg
2. 2.5 to 4.0 kg
3. 2.0 to <2.5 kg
4. 1.5 to <2.0 kg
5. <1.5 kg

Weight and gestation groups
1. <2.5 kg birth weight, either <37 wk (AGA) or >37 wk (SGA) gestation
2. >4.0 kg birth weight, either <42 wk (LGA) or ≥42 wk (AGA) gestation

Congenital variants
1. Twins
2. Anomalous male genitalia
3. Extra digits
4. Anencephaly
5. Cleft palate
6. Down's syndrome

Perinatal problems
1. Hyperbilirubinemia
2. ABO incompatibility
3. Respiratory distress (tachypnea, intercostal retractions, physical evidence of difficulty breathing)
4. NICU (Transfer to neonatal intensive care unit)
5. Infant of diabetic mother (insulin-dependent)
6. Hypoglycemia (blood glucose <40 mg/100 ml)
7. Meconium-stained amniotic fluid

delivery was established from the description in the infant's delivery record and confirmed when necessary by contacting the delivering physician. Congenital variants were determined by the attending physician in the nursery (members of the Departments of Pediatric and Family Medicine), who also were responsible for diagnosing those conditions included in the perinatal problems group.

The collection of cord blood, as well as the laboratory studies performed on the cord sera samples, was done by methods previously described (20). It should be noted that all studies were not performed on every cord serum sample because the amounts of cord blood, which could be obtained at delivery, were not adequate. Consequently, data are reported only for those samples that were assayed for the specific component being studied.

Data were analyzed by the Statistical Analyses System (SAS Institute, Inc., Carey, NC) for the analyses of variance by the Kruskal-Wallis test and by the General Linear Models Procedure utilizing Duncan's Multiple Range Test and the least square means options (11). For the presented analyses, infants with anencephaly or respiratory distress were excluded from all comparisons in Tables 3 and 4. Values for Duncan test are reported at $P \leq 0.05$ level.

RESULTS

The effects of various methods of delivery are shown for infants delivered by C-section (initial, repeat, and breech) and vaginal breech presentation (Table 2). In addition, the data for both the entire population and those described as normal vaginal deliveries are compared. The weight and gestation of all groups were essentially the same as the normal population except for the infants delivered by vaginal breech who were both smaller and younger. Significant changes were found in lipid values for three major groups. The normal vaginal delivery group had slightly higher triglyceride levels when compared with the total population. Infants delivered by C-section also had changes in the triglyceride levels, which were lower for both initial and repeat deliveries. The total cholesterol level was significantly lower only for infants delivered by initial C-section. A greater effect was demonstrated for vaginal breech delivery where both total cholesterol and lipid phosphorus were increased as were triglyceride and cholesterol ester levels, thus, vaginal breech delivery has the most impact upon cord sera lipid levels.

Cord sera apolipoprotein levels were also affected in the same groups of infants. Normal vaginal delivery was associated with significant decreases in A-I and A-II and a significant increase in ApoD when compared with the population. The effect of C-section was unusual in that ApoB levels were decreased significantly for initial C-section but not for repeat C-section. At the same time A-II and C-II levels were increased with a decrease in ApoD in infants delivered by repeat C-section. Vaginal breech delivery was associated with significant increases in both A-I and A-II whereas there was a significant decrease in ApoD. In summary, the method by which an infant is delivered appears to have a significant effect upon both cord sera lipid and apolipoprotein levels although the effects appear to be quite complex.

Multiple-range testing further defined the effects of vaginal and C-section delivery upon serum lipids and apolipoproteins. Vaginal delivery (cephalic or breech) significantly increased triglycerides when compared to C-section; however, vaginal breech delivery was associated with increased total cholesterol as expected on the basis of weight and gestational age. The same effect was also shown for apolipoproteins, with increased A-I and decreased ApoD. The ApoC-peptides were changed by delivery method because repeated C-section was associated with increased C-II but decreased C-III levels, whereas vaginal breech showed increased C-III levels. Factors to be described in subsequent tables will help explain some of the changes produced by the method of delivery.

In Table 3 the effects of weight on lipids and apolipoproteins were evaluated for five and four groups, respectively. The weights and gestational ages for each group were significantly different ($P < 0.0001$) from the normal and total population. In addition, each group was significantly different from the other groups for the same factors when tested by Duncan's Multiple Range Test.

For the lipids, weight alone produced no consistent effects. Triglyceride levels were increased in the >4.0 kg group and decreased in the 2.0 to <2.5 kg group with no difference for the other groups. Cholesterol data were also inconsistent because total cholesterol was increased in the <1.5 kg group whereas free cholesterol was increased for both the >4.0 kg and the 1.5 to <2.0 kg groups but decreased for the 2.5 to <4.0 kg group. Duncan's test showed that triglyceride levels were higher in the 1.5 to <2.0 kg and >4.0 kg groups than in the 2.0 to <2.5 kg group. Using the same test, total cholesterol was significantly higher in the <1.5 kg group than all other groups as was free cholesterol in the 1.5 to <2.0 kg group.

Apolipoprotein values demonstrated significant changes in several weight groups. As shown in Table 3, both A-I and A-II levels varied significantly with weight, but the changes were quantitatively small and did not differ when tested by Duncan's test. ApoB was increased in the <2.0 kg and decreased in the 2.5 to <4.0 kg groups, a significant difference confirmed by Duncan's testing between these two groups. All ApoD values showed significant variation with weight, but only the 2.5 to <4.0 kg group was different (higher) significantly from the other groups.

The combined effects of weight and gestation are presented in Table 4. Two separate weight groups are presented, specifically a small infant group weighing less than 2.5 kg and a large infant group weighing more than 4.0 kg. These two groups were subdivided according to gestational age. As noted in Table 4, weight and gestational age for each subgroup were significantly different from both the total population and the normal population except for gestational age in the group weighing more than 4.0 kg but less than 42 wk gestation.

The small infant group was subdivided into those infants with gestation less than 37 wk (AGA, prematurity) and greater than 37

Table 2. *Serum lipids by delivery mode*

	Weight (kg)	Gestational age (wk)	Triacyl-glycerol (mg/100 ml)	Cholesterol (mg/100 ml)			Lipid phosphorus (mg/100 ml)
				Total	Free	Ester	
Population	3.21 (0.69)[1]	39.2 (2.4)	38.9 (18.2)	70.2 (18.1)	17.2 (6.8)	54.8 (13.9)	4.85 (1.15)
N	1626[2]	1622	2042	2043	604	604	602
Normal vaginal	3.34 (0.36)	39.3 (0.5)*	41.4 (17.4)*	70.4 (16.3)	16.6 (5.1)	54.1 (12.1)	4.83 (1.81)
N	533	533	445	446	320	320	320
Caesarean section							
Initial	3.31 (0.76)*	39.4 (2.3)	37.4 (18.5)*,000	67.44 (19.6)**,00	18.3 (8.0)	51.7 (17.6)	4.72 (1.21)
N	193	199	189	189	41	41	41
Repeat	3.26 (0.54)[0]	39.3 (1.2)	31.8 (16.4)***,000	68.1 (13.5)	15.1 (5.1)	51.7 (10.4)	4.49 (0.75)
N	109	106	106	106	9	9	9
Breech	3.16 (0.74)	39.1 (2.8)	34.9 (17.5)	69.0 (17.1)	ND[3]	ND	ND
N	34	34	32	32			
Breech (vaginal)	2.79 (0.85)***,000	38.0 (3.6)*,000	45.8 (20.9)**	78.(18.4)***,00	19.9 (5.6)	67.4 (12.1)**,00	5.59 (0.58)*,0
N	54	53	53	53	7	7	7

	Apolipoproteins by delivery mode, values given in mg/100 ml							
	A-I	A-II	ApoB	C-I	C-II	C-III	ApoD	ApoE
Population	67.9 (22.3)	38.9 (12.4)	28.4 (9.1)	5.9 (2.2)	3.2 (1.1)	6.5 (2.6)	3.7 (1.4)	8.4 (3.3)
N	196	174	563	103	76	174	157	191
Normal vaginal	60.3 (29.1)*	33.0 (15.4)*	28.6 (8.9)	6.2 (2.5)	2.9 (1.0)	6.8 (2.8)	4.9 (1.3)*	8.2 (3.2)
N	50	44	232	51	30	59	49	61
Caesarean section								
Initial	62.3 (26.9)	36.4 (1.62)	26.7 (10.8)*,0	5.8 (1.1)	4.0 (2.0)	6.9 (2.7)	3.6 (1.8)	8.9 (3.9)
N	14	14	59	7	6	14	11	15
Repeat	69.4 (8.6)	43.8 (8.4)*	25.5 (5.6)	4.6	4.5 (1.2)*	5.8 (1.9)	2.6 (0.4)***	9.1 (2.9)
N	19	19	28		6	17	18	18
Breech	ND	ND	24.4 (10.8)	ND	ND	ND	ND	ND
N			7					
Breech (vaginal)	87.4 (21.8)*,0	46.8 (7.2)[0]	30.9 (10.5)	8.0	3.0 (0.3)	9.0 (4.2)	2.7 (0.5)000	9.7 (2.4)
N	7	5	15		2	6	5	7

[1] Mean (S.D.)
[2] Number
[3] Not determined
[4] Subgroup *vs* Population: $*P < 0.05$; $**P < 0.01$; and $***P < 0.001$.
[5] Subgroup *vs* Normal: $^{0}P < 0.05$; $^{00}P < 0.01$; and $^{000}P < 0.001$.

wk (SGA). The former group had significantly lower triglyceride levels with higher total cholesterol and free cholesterol levels, whereas for the latter group no significant difference in the lipid levels was observed when compared either to the total population or to normal infants. For small infants, a longer gestational age was associated with increased levels of apolipoproteins except for A-I and C-III, which were essentially unaffected, and ApoD, which was decreased in both groups of small infants. Infants weighing less than 2.5 kg and being less than 37 wk gestation had significant increases in A-II, ApoB, C-II, and ApoE levels with a significant decrease in ApoD. Infants weighing less than 2.5 kg but more than 37 wk gestation had significant decreases in C-I, ApoD, and ApoE when compared either to the normal or to the total population. When the two groups of infants weighing less than 2.5 kg were compared with each other by the Duncan's Multiple Range Test, the infants with gestational age of greater than 37 wk were heavier, had longer gestational ages, and had lower levels of ApoB, C-II, and ApoE.

The large infant group was divided into those infants less than 42 wk (LGA) and those of 42 wk or greater gestation (AGA). The cord sera lipid levels were unaffected by the infants' high birth weights with only triglyceride increasing significantly in those infants greater than 42 wk gestation. The apolipoprotein levels were minimally affected as well except for C-I levels (slightly increased in large infants less than 42 wk gestation) and for ApoD levels, which were lower for both groups and described in Table 3 as related to a weight greater than 4.0 kg. The marked effects of low birth weight and decreased gestational age upon cord sera lipid and apolipoprotein levels are thus not reflected in large infants no matter what their gestational age. Comparisons between the two groups (>4.0 kg) demonstrated significant differences only with respect to gestational age and triglyceride. Adjusting for weight and gestational age effects by least squares analysis, differences in triglyceride ($P = 0.056$), ApoD ($P = 0.057$) and ApoE ($P = 0.069$) were observed.

In Table 5 the effects of what are described broadly as congenital variants are presented. The variants included are twin births, anomalous male genitalia (either hypospadias or hydrocele), extra digits, anencephaly, cleft palate, and Down's syndrome. For the various groups, weight and gestational age were generally similar to both the normal and total populations. Twins, as expected, were both smaller and younger in gestational age; the groups predominantly male were heavier; and, predictably, anencephalic infants were lighter in weight.

Lipid levels were significantly different for only two groups. Twin infants had a significant decrease in triglyceride and a significant increase in total cholesterol similar to what was observed in premature infants. Anencephaly was associated with elevated levels of cholesterol. For this group total cholesterol, free cholesterol and cholesterol ester were all markedly increased although only a small number of infants were included because of the rarity of this problem.

Apolipoprotein levels were abnormal for the same two clinical groups exhibiting elevated lipids. Twin births had increased levels of C-III and decreased levels of ApoE. Anencephaly was associated with marked increases in all measured apolipoproteins except for the single observation of ApoD which was within the normal range.

Table 3. *Serum lipids by weight*

	Weight (kg)	Gestational age (wk)	Triacylglycerol (mg/100 ml)	Cholesterol (mg/100 ml)			Lipid phosphorus (mg/100 ml)
				Total	Free	Ester	
>4.0 kg	4.33 (0.29)[1], ***, 000	40.7 (1.6)***, 000	43.4 (21.7)**	72.7 (23.9)	20.0 (11.4)^{0}	56.4 (22.9)	4.90 (1.16)
N	171[2]	170	154	154	60	60	60
2.5–4.0 kg	3.31 (0.37)***	39.8 (1.5)***	39.4 (18.6)	69.7 (15.9)	16.5 (5.0)***	54.2 (11.9)	4.82 (1.12)
N	1177	1170	1048	1049	475	475	473
2.0–<2.5 kg	2.30 (0.14)***, 000	37.0 (2.1)***, 000	34.8 (17.8)***, 000	73.9 (20.4)*	18.5 (7.9)	55.5 (17.3)	4.87 (1.65)
N	159	156	148	148	28	28	28
1.5–<2.0 kg	1.78 (0.15)***, 000	35.3 (2.8)***, 000	45.7 (29.2)	73.9 (22.6)	28.4 (20.3)*, 0	55.9 (12.7)	5.29 (0.94)
N	42	42	35	35	7	7	7
<1.5 kg	1.25 (0.29)***, 000	30.3 (3.7)***, 000	40.9 (24.6)	86.4 (24.7)**	ND[3]	ND	ND
N	12	12	11	11			

	Apolipoproteins by weight, values given in mg/100 ml							
	A-I	A-II	ApoB	C-I	C-II	C-III	ApoD	ApoE
>4.0 kg	75.9 (20.5)^{0}	40.8 (7.2)^{0}	29.5 (8.6)	7.2 (1.6)	3.1 (0.9)	7.1 (2.0)	3.1 (0.9)^{000}	9.2 (3.1)
N	15	11	64	6	6	15	12	16
2.5–4.0 kg	65.7 (24.6)	37.9 (13.9)	27.9 (8.8)*	6.0 (2.4)	3.1 (1.0)	6.6 (2.8)	4.0 (1.5)**	8.2 (3.1)
N	112	102	396	74	51	113	99	123
2.0–<2.5 kg	65.2 (18.2)	40.5 (11.4)^{00}	28.8 (9.6)	5.1 (1.3)	3.5 (1.5)	6.3 (2.5)	3.2 (1.1)*, 000	8.3 (3.9)
N	33	29	49	15	14	29	29	32
<2.0 kg	70.8 (13.2)	39.0 (4.9)^{0}	32.4 (7.9)*, 0	4.4 (1.3)	4.0	6.4 (2.2)	2.9 (0.8)^{000}	9.5 (2.7)
N	10	8	19	2		5	7	9

[1] Mean (S.D.)
[2] Number
[3] Not determined
[4] Subgroup *vs* Population: $*P < 0.05$; $**P < 0.01$; and $***P < 0.001$.
[5] Subgroup *vs* Normal: $^{0}P < 0.05$; $^{00}P < 0.01$; and $^{000}P < 0.001$.

In Table 6, infants who either had or subsequently developed a variety of perinatal problems were studied. These problems included infants with diagnoses of hyperbilirubinemia, ABO incompatibility, respiratory distress, transfer to a neonatal intensive care unit, infant of a diabetic mother, hypoglycemia, and infants with meconium-stained amniotic fluid. As shown, the weights and gestational ages for each group were about as expected. For example, infants who subsequently developed RD were both smaller and less mature than those in the normal group, whereas the infants of diabetic mothers were heavier with only a slight decrease in gestational age.

Lipid levels were somewhat surprising in that a significant decrease in triglyceride levels was found in all conditions except meconium-stained amniotic fluid where triglycerides were significantly increased. Although the infants with decreased triglyceride levels were smaller and less mature than the total population, the same decreased levels were found in infants of diabetic mothers whose weight was significantly greater than that of the total population. Cholesterol and lipid phosphorous levels were increased in hyperbilirubinemia as seen with prematurity.

Apolipoprotein values were difficult to define in these groups because of the small numbers involved. Infants with respiratory distress demonstrated a significant decrease in ApoB levels with an almost significant decrease in ApoD ($P = 0.055$). Infants transferred to a neonatal intensive care unit and infants of diabetic mothers had decreased C-III and ApoD levels in spite of a very limited number of patients being included in each group. The most interesting finding was the decrease in ApoB levels in infants with RD, a condition known to be associated with prematurity and consequently a situation in which increased levels of ApoB would have been expected.

Because of that unexpected association, a more complete evaluation of lipids and apolipoproteins in infants with RD was performed and the data are presented in Table 7. To further explore the changes with RD, a comparison was made between three groups of infants. The first data are for infants less than 2.5 kg birth weight and less than 37 wk gestation who developed no respiratory distress after delivery. The second group repeats the data for all infants with RD shown in Table 6 and the last data shown are for infants of the same weight and gestation limits as the first group but who developed RD in the perinatal period. Serum lipid levels were lower for all lipids studied in both groups with RD when compared to premature infants without RD. The same changes were found for apolipoprotein levels but only ApoB levels were significantly lower in the RD groups. Regression analysis with weight and gestational age controlled confirmed the reduction in ApoB levels ($P < 0.03$) and also showed that A-II ($P < 0.03$) was also present at lower levels in infants who developed RD.

In an attempt to clarify the relationship between cord sera ApoD levels and triglyceride levels, the mean values for a variety of disorders were plotted (Fig. 1). A linear relationship between ApoD and triglycerides was found ($r = 0.84$, $P < 0.001$) if vaginal breech delivery and postmaturity (>4.0 kg, ≥42 wk) are excluded, both conditions being associated with fetal stress. These results suggest that ApoD may relate directly to serum triglyceride levels.

Regression analyses using weight and gestational age as the independent variables for the total population are summarized (Table 8). Controlling for gestational age, increasing birth weight was associated with increasing levels of free cholesterol, C-I, C-III, and ApoE with no significant decrease found for either lipids or apolipoproteins. Controlling for weight, increasing gestational age was associated with increasing levels of triglycerides and ApoD (in agreement with the relationship described in Fig. 1), but decreasing levels of total cholesterol, free cholesterol, A-II, C-II, and ApoE. Special note should be taken of the differing effects of weight and gestational age on free cholesterol, ApoE and the ApoC peptides. Free cholesterol and ApoE increase as weight increases, but decrease as gestational age increases, despite the positive correlation between birth weight and gestational age. In the same manner, C-I and C-III increased with weight, but C-II decreased with gestational age. Although neither weight nor ges-

Table 4. *Serum lipids by weight and gestational age*

	Weight (kg)	Gestational age (wk)	Triacyl-glycerol (mg/100 ml)	Cholesterol (mg/100 ml)			Lipid phosphorus (mg/100 ml)
				Total	Free	Ester	
Small infant group							
<2.5 kg <37 wks (AGA)	1.95 (0.39)[1, ***, 000]	33.9 (2.5)***, 000	34.9 (18.0)***, 000	75.4 (22.6)***, 00	23.9 (16.0)*, 0	60.3 (24.4)	5.12 (1.61)
N	144[2]	144	131	131	17	18	17
<2.5 kg >37 wks (SGA)	2.26 (0.24)***, 000	39.1 (1.0)**, 000	40.0 (24.8)[0]	70.9 (17.1)	17.6 (4.7)	ND[3]	4.72 (1.54)
N	76	76	68	68	18		18
Large infant group							
>4.0 kg <42 wks (LGA)	4.33 (0.32)***, 000	39.8 (0.9)**	40.3 (20.0)	72.2 (26.9)	20.4 (12.8)	55.7 (25.7)	4.92 (1.23)
N	116	116	102	102	46	46	46
>4.0 kg ≥42 wks (AGA)	4.33 (0.23)***, 000	42.7 (1.0)***, 000	49.2 (23.8)***	74.0 (17.1)	19.2 (5.2)	59.2 (9.2)	4.82 (0.93)
N	54	54	51	51	13	13	13

	Apolipoproteins by weight and gestational age, values given in mg/100 ml							
	A-I	A-II	ApoB	C-I	C-II	C-III	ApoD	ApoE
Small infant group								
<2.5 kg <37 wks (AGA)	66.3 (19.5)	41.2 (11.8)[00]	32.1 (10.0)**, 0	5.0 (1.9)	4.4 (1.3) **, 00	6.3 (2.7)	2.8 (1.2)**, 000	10.1 (3.8)*, 0
N	24	20	44	8	8	20	20	23
<2.5 kg >37 wks (SGA)	62.4 (13.1)	35.3 (7.7)	25.4 (6.9)	4.6 (1.2)*, 0	2.9 (1.2)	5.6 (1.5)	3.4 (0.9)[000]	6.6 (3.5)*
N	16	16	23	8	8	11	15	15
Large infant group								
>4.0 kg <42 wks (LGA)	76.2 (26.0)	40.7 (5.6)	29.0 (9.3)	8.3 (1.5)*	3.0 (1.4)	7.6 (2.3)	3.4 (1.1)[00]	8.6 (1.9)
N	8	5	41	3	2	7	7	8
>4.0 kg ≥42 wks (AGA)	75.6 (13.7)	40.9 (8.9)	30.5 (7.2)	6.1 (0.7)	3.2 (0.9)	6.6 (1.8)	2.6 (0.5)[000]	9.7 (4.0)
N	7	6	23	3	4	8	5	8

[1] Mean (S.D.)
[2] Number
[3] Subgroup *vs* Population: $*P < 0.05$; $**P < 0.01$; and $***P < 0.001$.
[4] Subgroup *vs* Normal: $^{0}P < 0.05$; $^{00}P < 0.01$; and $^{000}P < 0.001$.

tational age alone significantly affected ApoB levels, consideration of gestational age and weight as interacting variables produced a significant ($P < 0.01$) correlation ($r = 0.120$) for ApoB.

DISCUSSION

Levels of lipids and apolipoproteins in cord sera should be a reflection of the status of plasma lipid metabolism in the infant at birth. The plasma lipid transport system *in utero* provides for the transport of lipids, that have not been absorbed from the intestine because amniotic fluid contains only small amounts of lipids (19) and the intestine is apparently unable to synthesize chylomicrons at birth (21). Most fetal lipids are synthesized *de novo* through the conversion of glucose to various fatty acid-containing compounds whereas part of the lipids are obtained from the maternal circulation by way of the placenta principally in the form of free fatty acids and free cholesterol (6). Because the deposition of triglyceride continues up to 40 wk gestation as weight rapidly increases (26), the rate of lipid metabolism must increase significantly. At the same time factors that normally modify lipid metabolism might have the same effects *in utero* and be expressed by changes in the serum lipids and apolipoproteins. This assumption has been confirmed in the current study and the various effects will be discussed.

Of the serum lipids, cholesterol has been studied more extensively because of its relationship to atherosclerosis. But cord blood levels of cholesterol have not been good predictors of childhood hypercholesterolemia as recently discussed (7), apparently because other factors are more important in determining serum cholesterol levels at birth. In particular, both weight and gestation have a significant effect upon the cholesterol levels with both factors related to cord sera cholesterol levels. The increase in serum cholesterol in cord blood is most obvious in premature infants (infants less than 2.5 kg and less than 37 wk gestation). Two conditions associated with prematurity, twin births and hyperbilirubinemia, were also associated with increased levels of cholesterol. The most extreme increase in serum cholesterol was associated with a severe congenital anomaly, anencephaly. Other workers have previously described this finding (23) and have ascribed the marked increase in cholesterol to the inhibition of cholesterol conversion to adrenocorticosteroids. Supporting evidence for this concept is the report of Benirschke (4), which describes the progressive involution of the fetal cortex after 20 wk gestation in fetuses with anencephaly.

The triglyceride levels in cord sera have been less well studied than those of cholesterol. As expected, triglyceride levels increased with increasing gestation, probably reflecting the progressive fatty deposition occurring during the latter stages of gestation. As might

Table 5. *Serum lipids by congenital variants*

	Weight (kg)	Gestational age (wk)	Triacyl-glycerol (mg/100 ml)	Cholesterol (mg/100 ml)			Lipid phosphorus (mg/100 ml)
				Total	Free	Ester	
Twins	2.50 (0.63)[1], ***, 000	37.8 (3.2)***	36.3 (18.2)00	75.0 (19.5)*	18.4 (6.2)	56.2 (12.4)	5.17 (1.68)
N	70[2]	70	70	70	15	15	15
Anomalaous Male genitalia	3.54 (0.52)	40.4 (1.3)	39.8 (20.3)	65.8 (14.7)	11.8 (5.1)	48.8 (6.8)	4.31 (0.97)
N	19	19	18	18	4	4	4
Extra digits	3.14 (0.76)	39.8 (1.4)	35.2 (20.6)	78.4 (33.2)	15.6 (6.2)	49.2 (13.0)	4.40 (0.77)
N	10	10	10	10	5	5	5
Anencephaly	1.87 (0.60)**, 000	38.0 (4.4)	33.5 (11.4)	184.0 (32.4)***, 000	52.0	112.0	7.87
N	4	4	4	4			
Cleft palate	3.22 (0.77)	40.9 (2.7)	45.3 (19.5)	64.7 (18.1)	ND[3]	ND	ND
N	7	7	6	6			
Down's syndrome	3.32 (0.23)	39.0 (2.5)	43.7 (19.8)	82.0 (26.8)	ND	ND	ND
N	6	6	6	6			

	Apolipoproteins by congenital variants, values given in mg/100 ml							
	A-I	A-II	ApoB	C-I	C-II	C-III	ApoD	ApoE
Twins	68.9 (19.3)	37.6 (9.0)	27.6 (7.8)	5.8 (0.9)	4.7 (3.0)	8.6 (1.7)*	3.5 (0.8)	6.8 (2.7)*
N	18	16	33	7	3	7	14	16
Anomalous Male genitalia	73.2 (18.3)	39.3 (6.6)	21.7 (4.9)	6.0	2.3	5.3 (0.3)	2.5 (0.5)	7.8 (2.1)
N	5	3	5			4	2	4
Extra digits	77.8 (14.2)	44.1 (14.0)	22.5 (12.3)	5.4	ND	5.8 (3.0)	3.8 (1.4)	9.9 (6.2)
N	3	3	3			3	3	3
Anencephaly	84.0 (6.5)	60.1	52.2 (18.5)**, 00	ND	ND	10.6 (3.4)	4.6	16.8
N	3		4			2		
Cleft palate	ND	ND	31.0	ND	ND	ND	ND	ND
N								
Down's syndrome	ND	ND	24.4	ND	ND	ND	ND	ND
N								

[1] Mean (S.D.)
[2] Number
[3] Not determined
[4] Subgroup *vs* Population: $*P < 0.05$; $**P < 0.01$; and $***P < 0.001$.
[5] Subgroup *vs* Normal: $^{0}P < 0.05$; $^{00}P < 0.01$; and $^{000}P < 0.001$.

be expected with a more metabolically active compound, the triacylglycerol levels also showed much greater variation at the time of birth. Increased levels were primarily associated with fetal distress (1, 12, 27), such as vaginal breech deliveries and where the amniotic fluid was stained with meconium. Birth weight was also associated with increased triglyceride levels because infants weighing greater than 4.0 kg at birth had significantly higher levels of triglyceride.

The major change of clinical significance in the serum triglycerides was the surprisingly frequent association of decreased triglycerides with a variety of perinatal disorders. There was a significant decrease in triglyceride level for both initial and repeat C-sections, which may indicate that some of these infants were delivered prematurely by C-section (10, 15) or that the trauma of passage through the birth canal increased the serum triglycerides in infants delivered vaginally. Prematurity was associated with significant decreases in triglyceride as were twin births, again demonstrating twinning's association with premature birth (17). The most unexpected decrease in triglyceride levels is found in infants who subsequently became ill or developed evidence of gestational immaturity. Significant decreases in triglyceride are found in association with hyperbilirubinemia, RD, infants subsequently transferred to a neonatal intensive care unit, infants of diabetic mothers, and hypoglycemia. On this basis, a decrease in cord serum triglycerides would appear to be of more importance in predicting ill infants than the increase in serum triglyceride associated with perinatal fetal distress.

The phospholipid (or lipid phosphorus) levels were affected very little by perinatal conditions. Except for vaginal breech delivery and hyperbilirubinemia there were no significant increases found in cord sera lipid phosphorus. This is in marked contrast to the significance of individual phospholipid levels in amniotic fluid where they are a predictor of lung maturity (3).

When compared to the cord serum lipids, the apolipoprotein levels displayed a much broader range of changes with various perinatal factors than did the lipids. The ApoA (A-I, A-II) polypeptides, the major components of high density lipoproteins, increased significantly in vaginal breech deliveries and in infants whose weight was greater than 4.0 kg. A-II alone was increased in infants delivered by repeat C-section and whose weight was less than 2.5 kg. This increase was most pronounced in premature infants (weight <2.5 kg, gestation <37 wk). The association of increased A-II with prematurity suggests that the increase in A-II is related to the increased serum cholesterol levels found in premature infants, especially in the high density lipoprotein fraction as reported by Hardell (16).

The changes in ApoB, the major protein of low density lipoproteins, were more complex than the changes in ApoA peptides. Increased levels of ApoB were found in premature infants but were independent of weight, suggesting that gestational age was the more important factor in producing the increased levels. The elevated ApoB concentration found in anencephaly was predictable, from its association with marked elevation of serum cholesterol, and agrees with the increased low density lipoproteins levels reported by Parker *et al.* (23). Reduced levels of ApoB were unexpectedly found in infants delivered by initial C-section; no explanation is readily available. Of more interest are the decreased levels of ApoB in RD, a condition frequently associated with

Table 6. *Serum lipids by perinatal problems*

	Weight (kg)	Gestational age (wk)	Triacyl-glycerol (mg/100 ml)	Cholesterol (mg/100 ml)			Lipid phosphorus (mg/100 ml)
				Total	Free	Ester	
Hyperbilirubinemia	3.02 (0.71)[1,*]	38.5 (2.5)***	32.8 (21.0)***,000	73.5 (14.3)*,0	20.2 (5.1)*	58.7 (13.7)	5.50 (1.53)*
N	88[2]	86	81	81	16	15	17
ABO incompatibility	3.23 (0.44)	39.3 (1.8)[0]	37.3 (16.9)	68.5 (17.3)	20.3 (2.3)	62.6 (2.5)	5.59 (0.58)
N	25	24	22	22	3	3	3
Respiratory distress	2.27 (0.74)***,000	35.4 (3.8)***,000	30.1 (14.6)***,000	70.0 (19.2)	18.8 (7.6)	55.3 (13.8)	4.53 (1.09)
N	61	59	59	59	6	6	6
NICU transfer	2.48 (0.72)***,000	36.7 (4.0)***,000	29.6 (19.3)**,000	67.4 (24.4)	38.0	88.0	6.70
N	18	18	20	20			
Infant of diabetic mother	3.71 (0.75)***,000	38.6 (2.2)000	32.6 (14.5)*,00	71.0 (24.1)	24.0	80.0	5.47
N	27	27	25	25			
Hypoglycemia	2.51 (0.96)[0]	35.8 (4.0)*,000	24.2 (3.6)*,0	89.0 (28.3)	38.0	88.0	6.70
N	4	4	4	4			
Meconium-stained amniotic fluid	3.33 (0.5)	39.8 (1.8)	58.3 (38.3)**,0	65.1 (24.9)	ND[3]	ND	ND
N	15	15	14	14			

	Apolipoproteins by perinatal problems, values given in mg/100 ml							
	A-I	A-II	ApoB	C-I	C-II	C-III	ApoD	ApoE
Hyperbilirubinemia	69.7 (16.0)	40.4 (11.5)	30.2 (8.3)	5.4 (2.0)	3.5 (0.9)	6.4 (2.3)	2.8 (0.8)	8.7 (3.5)
N	23	19	30	7	6	19	18	21
ABO incompatibility	31.0	17.0	24.5 (4.0)	6.0	4.6	8.2	3.0	10.0
N			4					
Respiratory distress	61.9 (18.6)	37.5 (15.2)	23.2 (6.7)[0]	4.3 (2.4)	4.2 (0.4)	5.0 (1.9)	2.6 (1.1)	9.0 (4.7)
N	6	6	10	3	3	6	6	6
NICU transfer	64.9 (18.9)	39.3 (7.6)	26.8 (8.2)	ND	3.8 (0.8)	4.2 (1.1)[0]	2.0 (0.9)*,00	9.9 (4.5)
N	3	3	4		2	3	3	3
Infant of diabetic mother	58.8 (10.2)	37.9 (4.1)	28.0 (10.0)	ND	ND	3.6 (1.1)	1.9 (0.2)**	8.0 (2.0)
N	4	4	6			2	3	2
Hypoglycemia	54.2	40.8	32.4 (8.0)	ND	ND	ND	2.1	14.2
N			2					
Meconium-stained amniotic fluid	ND	ND	23.6 (9.4)	ND	ND	ND	ND	ND
N			2					

[1] Mean (S.D.)
[2] Number
[3] Not determined
[4] Subgroup *vs* Population: $*P < 0.05$; $**P < 0.01$; and $***P < 0.001$.
[5] Subgroup *vs* Normal: $^{0}P < 0.05$; $^{00}P < 0.01$; and $^{000}P < 0.001$.

premature birth in which increased ApoB levels were found in this study.

The ApoC polypeptides (C-I, C-II, C-III) present a highly variable response to the various perinatal factors. C-I was related to birth weight with progressively decreasing levels in infants weighing less than 4 kg. This change is most obvious in infants who are either small for gestational age or large for gestational age, suggesting that the C-I is related to some factor determining birth weight. Because triglyceride deposition is the major variable as far as birth weight differences are concerned, it is possible that C-I plays a role in the triglyceride changes that occur just before birth.

The other two C-peptides (C-II and C-III) are relatively unaffected by perinatal conditions. C-II peptide levels fell progressively with increasing gestational age and were increased with both prematurity and weight less than 2.5 kg. Because C-II is known to be a cofactor in the lipoprotein lipase reaction (22), the progressively falling levels of C-II with increasing gestational age and triglyceride levels would indicate that the level of C-II might play a role in determining the triglyceride level. ApoC-III does not appear to have any meaningful relationship with any of the perinatal factors studied.

Another unexpected finding was the significant relationship between the cord sera ApoD values and a variety of perinatal factors including conditions that developed after birth. All of the changes are associated with decreased levels of ApoD. Infants who subsequently developed RD, who were transferred to a neonatal intensive care unit, or who were infants of diabetic mothers had reduced levels of ApoD at delivery. No unifying concept can explain the complexity of these changes, although the severity of the associated conditions indicates that more extensive studies of ApoD are needed to establish its value as a diagnostic tool.

Of the apolipoproteins only ApoE has the relationship expected from adult ApoE studies. For infants weighing less than 2.5 kg, a gestational age of less than 37 wk is associated with increased ApoE levels and a gestational age greater than 37 wk is associated with decreased ApoE levels. This confirms the negative correlation between ApoE levels and gestational age *i.e.*, as gestational age increases, ApoE levels progressively decrease. Because ApoE has a well established relationship to cholesterol metabolism (8, 18), this progressive fall correlates well with the decreasing cholesterol levels of increasing gestational age. The increasing ApoE levels with increasing weight (when controlled for gestation) probably reflect progressive deposition of lipid in body tissues.

Because of the clinical importance of neonatal RD, lipid changes in this disorder were more extensively evaluated than other disorders. The decreased levels of serum triglyceride in RD were appropriate for age and weight at birth. What was not expected was a significant decrease in both total cholesterol and ApoB in infants with RD. Based on gestational age the levels of total cholesterol should have been increased significantly and the

Table 7. *Comparison of cord sera lipids from respiratory distressed and premature infants*

	Weight (kg)	Gestational age (wk)	Triacyl-glycerol (mg/100 ml)	Total cholesterol (mg/100 ml)	Unesterified cholesterol (mg/100 ml)	Lipid phosphorus (mg/100 ml)
No respiratory distress (<2.5 kg, <37 wks)	2.01 (0.37)	34.3 (2.3)	36.9 (19.4)	79.9 (23.9)	27.0 (17.3)	5.52 (1.64)
N	112	112	101	101	16	16
Respiratory distress	2.26 (0.74)	35.4 (3.8)	30.1 (14.6)*	70.0 (19.2)*	18.8 (7.6)	4.52 (1.09)
N	61	59	59	59	6	6
Respiratory distress (<2.5 kg, <37 wks)	1.72 (0.38)	32.6 (2.6)***	29.0 (10.1)	67.7 (21.0)*		
N	33	33	31	31		

	Comparison of cord sera apolipoproteins from respiratory distressed and premature infants, given in mg/100 ml							
	A–I	A–II	ApoB	C–I	C–II	C–III	ApoD	ApoE
No respiratory distress (<2.5 kg, <37 wks)	69.8 (19.7)	43.6 (11.3)	34.1 (10.0)	5.5 (1.4)	4.5 (1.5)	7.2 (3.0)	3.0 (1.2)	10.4 (3.4)
N	21	16	39	7	6	17	16	19
Respiratory distress	61.8 (18.6)	37.5 (15.2)	23.2 (6.7)**	4.3 (2.4)	4.2 (0.4)	5.0 (1.9)	2.6 (1.1)	9.0 (4.7)
N	6	6	10	3	3	6	6	6
Respiratory distress (<2.5 kg, <37 wks)	54.1 (11.3)	31.8 (10.2)	21.1 (6.1)**	1.6	4.0 (0.5)	4.0 (1.1)	2.0 (0.8)	8.8 (5.7)
N	4	4	5		2	4	4	4

*$P < 0.05$
**$P < 0.01$ * } Comparison between RD and premature (No RD)
***$P < 0.001$

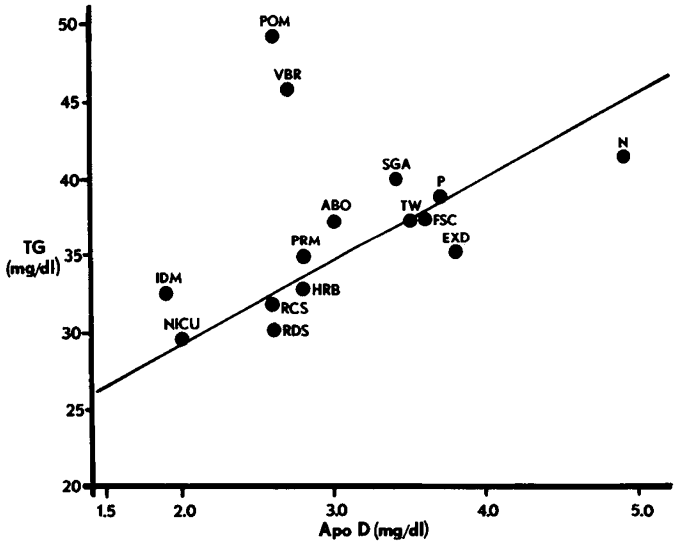

Fig. 1. Relation between triglycerides and ApoD. TG, triacylglycerol; ApoD, apolipoprotein D; P, mean values for population; N, normal vaginal; FCS, initial caesarean section; RCS, repeat caesarean section; VBR, vaginal breech; PRM, Premature; SGA, small for gestational age; POM, postmature; TW, twins; EXD, extra digits; HRB, hyperbilirubinemia; ABO, ABO incompatibility; RDS, respiratory distress; NICU, transfer to neonatal intensive care unit; and IDM, infant of diabetic mother.

ApoB levels should have been comparable to those of small immature infants without RD. These decreased levels of triglycerides, total cholesterol, and ApoB suggest that there is a deficiency of lipid substrate necessary for the formation of pulmonary surfactant, which requires fatty acids and some cholesterol for its formation (3). This could explain the response to betamethasone in reducing the frequency of RD because corticosteroids are known to increase production of very low density lipoproteins (2, 25), which in turn would then increase the substrate available for surfactant. This finding also suggests the possibility of a specific

Table 8. *Regression analysis of cord serum lipids and apolipoproteins predicted by gestational age and weight*

	Slope	*P*	*r*
Weight[1]			
FC	1.18	0.0437	0.198
C–I	1.46	0.0011	0.336
C–III	0.92	0.0247	0.174
ApoE	1.10	0.0133	0.255
Gestation[2]			
TG	1.56	0.0001	0.170
TC	−0.68	0.0086	0.083
FC	−0.92	0.0001	0.198
A–II	−1.00	0.0585	0.157
C–II	−0.23	0.0024	0.372
ApoD	0.19	0.0015	0.275
ApoE	−0.46	0.0005	0.255
Weight and gestation[3]			
ApoB	0.54	0.0100	0.120

[1] Corrected for gestational age.
[2] Corrected for weight.
[3] Interaction of weight and gestation.

therapy, that is, exchange transfusion to increase the levels of lipids and apolipoproteins. In fact, data indicating improvement of respiratory distress syndrome with exchange transfusion are available (13) although other complications may arise.

An unexpected relationship also existed between the levels of cord sera triglyceride and ApoD values. ApoD had been reported to be involved in the lecithin cholesterol acyl transferase reaction (9). The close correlation between ApoD and triglyceride levels suggests that ApoD may play a specific role in triglyceride metabolism as discussed by Chajek and Fielding (9), perhaps as an acyl carrier protein. More extensive evaluation of this relationship is obviously needed.

Overall, gestational age has a major impact upon the levels of both lipids and apolipoproteins at the time of delivery. Cholesterol

(total and free) and ApoE can be shown to decrease progressively with increasing gestational age. Triglycerides increase with increasing gestational age, reflecting increases in total body fat during the latter stages of gestation (26). The increase in triglyceride was compatible with the increase in weight and the decrease in C-II with increasing gestation. ApoD levels clearly increase with gestational age and are related directly to increases in serum triglycerides. The possibility that ApoD also relates to falling cholesterol levels cannot be ruled out, but changes in ApoD in this study are associated with clinical conditions relating more to triglyceride metabolism than to cholesterol metabolism.

In conclusion, it is clear that cord sera lipid and apolipoprotein levels are products of multiple factors including duration of gestation, method of delivery, and many metabolic states. More data about specific functions of the apolipoproteins are needed before their diagnostic value in the cord sera can be established. Certainly, these results indicate that a more extensive evaluation should provide new information about the functional role of apolipoproteins and be helpful in developing a better understanding of the energy metabolism of the infant at birth.

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28. Informed consent was not required by the Human Experimentation Committee, University of Oklahoma Health Sciences Center, for this study because cord blood was considered to be a salvage product of delivery.

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30. Requests for reprints should be addressed to: Walter J. McConathy, Ph.D., Laboratory of Lipid and Lipoprotein Studies, Oklahoma Medical Research Foundation, 825 N.E. 13th Street, Oklahoma City, Oklahoma 73104 (U.S.A.).

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