heterozygous for familial hypercholesterolemia. Amer. J. Dis. Child., *131*: 162 (1977).
12. Lipid Research Clinics Program: Manual of Laboratory Operations, Vol. 1 (United States Government Printing Office, Washington, D.C., 1974).
13. Snedecor, G. W., and Cochran, W. G.: Statistical Methods, Ed. 6, p. 128 (Iowa State University Press, Ames, Iowa, 1967).
14. Snedecor, G. W., and Cochran, W. G.: Statistical Methods, Ed. 6, p. 172 (Iowa State University Press, Ames, Iowa, 1967).
15. Snedecor, G. W., and Cochran, W. G.: Statistical Methods, Ed. 6, p. 194 (Iowa State University Press, Ames, Iowa, 1967).
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High density lipoprotein cholesterol (C-LDL)
low density lipoprotein cholesterol (C-HDL)
neonate

Low and High Density Lipoprotein Cholesterol Interrelationships in Neonates with Low Density Lipoprotein Cholesterol ≤ the 10th Percentile and in Neonates with High Density Lipoprotein Cholesterol ≥ the 90th Percentile

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Summary

Since the inverse relationship between high density lipoprotein cholesterol (C-HDL) and low density lipoprotein cholesterol (C-LDL) is generally recognized in school children and in adults, but not at birth, the current study was focused on neonates having C-HDL ≥ the 90th percentile and neonates with C-LDL ≤ the 10th percentile to determine whether any distinctive relationships existed at the extreme limits of the frequency distribution among C-HDL, C-LDL, and total plasma cholesterol. Sixty-three neonates with C-LDL ≤ the 10th percentile (20 mg/dl), and 58 with C-HDL ≥ the 90th percentile (50 mg/dl) were selected in the consecutive order of their birth as part of an ongoing cord blood lipid and lipoprotein survey. Comparisons of the hypobeta- and hyperalphalipoproteinemic neonates with 117 previously described unselected neonates were made. In the 117 unselected neonate controls, both C-HDL and C-LDL levels were closely correlated with total cord blood cholesterol ($r = 0.63$, 0.76, $P < 0.01$), whereas C-HDL was not significantly related to C-LDL ($r = 0.002$). In the 63 hypobetalipoproteinemic neonates, C-HDL correlated closely with total plasma cholesterol concentrations ($r = 0.98$, $P < 0.01$). C-LDL failed to correlate with total plasma cholesterol ($r = 0.07$). In the face of low cord blood C-LDL, nearly all of the total plasma cholesterol variation was accounted for by C-HDL. C-HDL was not significantly related to C-LDL ($r = -0.15$). In 58 hyperalphalipoproteinemic neonates, C-HDL did not significantly correlate with total cholesterol concentrations ($r = 0.22$), whereas C-LDL was closely related ($r = 0.88$, $P < 0.01$), with nearly all of the total plasma cholesterol variation accounted for by C-LDL. The inverse C-HDL to C-LDL relationship was not significant ($r = -0.18$)

Speculation

Whatever factors contribute to both the overall and to the extremes of the C-HDL and C-LDL frequency distributions at birth, C-HDL and C-LDL in neonates appear to be under independent metabolic control.

Plasma high density lipoprotein cholesterol levels in adults are often inversely correlated with low density lipoprotein cholesterol levels (1, 3, 7, 8). In the Bogalusa lipoprotein study in white and black school children, total plasma cholesterol and C-LDL levels were closely correlated ($r = 0.745$, 0.727) (12). Total plasma cholesterol also correlated with C-HDL concentrations in whites and blacks ($r = 0.441$, $r = 0.595$) (12). The Bogalusa study (12) revealed significant inverse relationships between C-HDL and C-LDL levels in 1174 black children ($r = -0.09$), and in 2009 white children ($r = -0.231$). The correlation in black children ($r = -0.09$) between C-HDL and C-LDL, although statistically significant, is low, and perhaps of doubtful biologic import. Rhoads *et al.* (9) found no significant correlation between C-HDL and C-LDL ($r = 0.01$) and concluded that "the inverse relation of alpha cholesterol to prevalence of coronary heart disease was independent of beta cholesterol . . . ." (9).

In cord blood, C-HDL accounts for about one-half of total plasma cholesterol (13), in contrast to older children (12) and adults (1, 2, 7, 8) where C-HDL makes up less than one-third of total plasma cholesterol levels. In our recent study of 117 unselected neonates, cord blood C-HDL levels did not correlate with C-LDL ($r = -0.002$), whereas C-HDL and C-LDL concentrations correlated closely with total plasma cholesterol ($r = 0.63$, $r = 0.76$, $P < 0.001$) (5). Since the inverse relationship between C-HDL and C-LDL is generally recognized in school children (12) and in adults (1, 3, 7, 8), but not at birth (5), the current study was focused on neonates having C-HDL ≥ the 90th percentile and neonates with C-LDL ≤ the 10th percentile to determine whether distinctive inverse relationships between C-HDL and C-LDL existed at the extreme limits of the frequency distribution.

MATERIALS AND METHODS

PATIENTS

Sixty-three neonates with C-LDL ≤ the 10th percentile (20 mg/dl) (13), and 48 with C-HDL ≥ the 90th percentile (50 mg/dl) (6) were selected in the consecutive order of their birth as part of an ongoing cord blood lipid and lipoprotein survey. Use of the 10th percentile (C-LDL) and the 90th percentile (C-HDL) for the identification of neonatal hypobeta- and hyperalphalipoproteinemia, although based on neonatal population data (6), was arbitrary, and might not be customarily synonymous with other definitions of the disorders. Cord blood cholesterol, C-HDL, and C-LDL were quantitated as previously described (16). There was no known bias in selection of the neonates who were entered into the study consecutively in order of their live birth, with informed parental consent. There was no selection on the basis of maturity, birth weight, or perinatal stress factors (15).

STATISTICAL ANALYSES

Comparisons of the hypobeta- and hyperalphalipoproteinemic neonates with 117 previously described unselected neonates (5) were made using the *t*-test (10). Relationships between lipid and lipoprotein classes were assessed by regression analysis (11).

RESULTS

C-HDL, C-LDL, AND TOTAL PLASMA CHOLESTEROL IN HYPOBETA-, HYPERALPHALIPOPROTEINEMIC NEONATES, AND CONTROL SUBJECTS

As summarized in Table 1, children selected by C-LDL ≤ 10th percentile had lower plasma total cholesterol levels, and similar plasma C-HDL levels when compared to the 117 unselected neonatal controls.

Children selected by C-HDL ≥ the 90th percentile had plasma total cholesterol levels which were higher, and plasma C-LDL levels which were lower than those in the 117 neonatal control subjects, $P < 0.01$.

C-HDL AND C-LDL RELATIONSHIPS: HYPOBETA- AND HYPERALPHALIPOPROTEINEMIC NEONATES AND CONTROL SUBJECTS

As summarized in Table 2, relationships between C-HDL and total cholesterol, C-LDL and total cholesterol, and C-HDL and C-LDL were different for control, hypobeta-, and hyperalphalipoproteinemic neonates. In the 117 unselected newborn control subjects, both C-HDL and C-LDL levels were closely correlated with total cord blood cholesterol ($r = 0.63$, $r = 0.76$, $P < 0.01$), whereas C-HDL was not significantly related to C-LDL ($r = -0.002$).

In the 63 hypobetalipoproteinemic neonates, C-HDL correlated closely with total plasma cholesterol concentrations ($r = 0.98$, $P < 0.01$). C-LDL failed to correlate with total plasma cholesterol ($r = 0.07$). C-HDL was not significantly related to C-LDL ($r = -0.15$), Table 2.

In 58 hyperalphalipoproteinemic neonates, C-HDL did not significantly correlate with total cholesterol concentrations ($r = 0.22$), while C-LDL was closely related ($r = 0.88$, $P < 0.01$), Table 2. The inverse C-HDL to C-LDL relationship was not significant ($r = -0.18$), Table 2.

Table 1. *High density lipoprotein cholesterol (C-HDL), total plasma cholesterol, and low density lipoprotein cholesterol (C-LDL) in 117 unselected control neonates, 63 neonates with C-LDL ≤ 20 mg/dl, and 58 neonates with C-HDL ≥ 50 mg/dl* ($\bar{x} \pm$ SE)

Subjects	C-HDL, mg/dl	Total plasma choelsterol, mg/dl	C-LDL, mg/dl
117 Unselected controls	35.5 ± 0.9	72.0 ± 1.4	30.2 ± 1.0
63 Neonates, C-LDL ≤ 20	33.7 ± 1.3	51.3 ± 1.2[1]	13.1 ± 0.2[1]
58 Neonates, C-HDL ≥ 50	59.1 ± 1.0[1]	86.4 ± 2.3[1]	22.6 ± 2.1[1]

[1] $P < 0.01$, as compared to 117 unselected control subjects.

Table 2. *Interrelationships between high density (C-HDL) and low density (C-LDL) lipoprotein cholesterol, and total plasma cholesterol levels: 117 unselected neonatal control subject, 63 neonates with C-LDL ≤ 20 mg/dl; 58 neonates with C-HDL ≥ 50 mg/dl*

Subjects	Correlation coefficient (r)		
	C-HDL: total plasma cholesterol,	C-LDL: total plasma cholesterol	C-HDL: C-LDL
117 Unselected controls	0.63[1]	0.76[1]	−0.002
63 Neonates, C-LDL ≤ 20	0.98[1]	0.07	−0.15
58 Neonates, C-HDL ≥ 50	0.22	0.88[1]	−0.18

[1] $P < 0.01$.

DISCUSSION

Marked quantitative differences exist for C-HDL and C-LDL in neonates compared with older children and adults (2, 4, 5, 12). Plasma C-HDL levels in children and adults are increased only by about 40–50% from those at birth, whereas C-LDL increases 4-fold (2, 4, 12–14). The ratio of C-HDL to C-LDL (about 1.2:1 at birth) (5) changes to 1:2.4 in adults (3, 4). In children and adults, both C-LDL and C-HDL correlate positively with total plasma cholesterol, whereas C-HDL usually, but not invariably (9), correlates inversely with C-LDL (1, 3, 7, 8, 12). This inverse correlation may be important since the C-HDL is thought to be "antiatherogenic" whereas C-LDL is the predominant atherogenic lipoprotein (3–6, 9).

In 117 unselected neonates the correlation coefficients for C-HDL to total cholesterol ($r = 0.63$), and C-LDL to total cholesterol ($r = 0.76$), were very similar to those reported for older children (12). The C-HDL to C-LDL relationship was not significant in the 117 neonates ($r = -0.002$), in contrast to the relationship in large groups of school children ($r = -0.231$ for 2009 whites, $r = -0.09$ for 1174 blacks (12).

In hypobetalipoproteinemic neonates, C-LDL failed to correlate with total plasma cholesterol, in contrast to unselected control neonates or older school children (12). However, C-HDL was closely related to total plasma cholesterol, resembling

the relationship in control neonates or older children. In the face of low cord blood C-LDL, nearly all of the total plasma cholesterol variation was accounted for by C-HDL. The inverse C-HDL to C-LDL correlation was not significant.

In hyperalphalipoproteinemic neonates, C-LDL but not C-HDL correlated significantly with total plasma cholesterol. Nearly all of the total plasma cholesterol variation was accounted for by C-LDL. The inverse C-HDL to C-LDL relationship was not significant.

Whatever factors contribute to both the overall and to the extremes of the C-HDL and C-LDL frequency distributions at birth, C-HDL and C-LDL in neonates appear to be under independent metabolic control.

It might be interesting to follow into later infancy and childhood neonates at the extreme of the C-LDL and C-HDL distributions to determine whether or when, with the inevitable ascendence of C-LDL as the predominant cholesterol carrying lipoprotein (1–4), significant inverse C-HDL to C-LDL relationships will appear.

CONCLUSION

In 117 unselected neonates the correlation coefficients for C-HDL to total cholesterol ($r = 0.63$), and C-LDL to total cholesterol ($r = 0.76$) were very similar to those reported for older children. However, in contrast to school children, the C-HDL to C-LDL relationship in the unselected neonates was not significant ($r = -0.002$). In 63 hypobetalipoproteinemic neonates, C-LDL failed to correlate with total plasma cholesterol levels ($r = 0.07$), but C-HDL was closely related to total cholesterol ($r = 0.98$). The inverse C-HDL to C-LDL correlation was not significant. In 58 hyperalphalipoproteinemic neonates C-LDL ($r = 0.88$), but not C-HDL ($r = 0.22$), correlated significantly with total plasma cholesterol. Nearly all of the total plasma cholesterol variation was accounted for by C-LDL. The inverse C-HDL to C-LDL relationship ($r = -0.18$) was not significant. Whatever factors contribute to both the overall and to the extremes of the C-HDL and C-LDL frequency distributions at birth, C-HDL and C-LDL in neonates appear to be under independent metabolic control.

REFERENCES AND NOTES

1. Carlson, L. A.: Lipoprotein fractionation. J. Clin. Path. Suppl. 5, *26:* 32 (1973).
2. Fredrickson, D. S., and Levy, R. I.: Familial hyperlipoproteinemia. In: J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson: The Metabolic Basis of Inherited Disease, Ed. 3, pp. 545–614 (McGraw-Hill Book Co., New York, 1972).
3. Glueck, C. J.: Alpha-lipoprotein cholesterol, beta-lipoprotein cholesterol, and longevity. Artery, *2*(3): 196 (1976).
4. Glueck, C. J., Gartside, P., Fallat, R. W., Sielski, J., and Steiner, P. M.: Longevity syndromes: Familial hypobeta- and familial hyperalphalipoproteinemia. J. Lab. Clin. Med., *88:* 941 (1976).
5. Glueck, C. J., Gartside, P. S., Tsang, R. C., Mellies, M. J., and Steiner, P. M.: Black-white similarities in cord blood lipids and lipoproteins. Metabolism, *26:* 347 (1977).
6. Glueck, C. J., Tsang, R. C., Mellies, M. J., and Steiner, P. M.: Neonatal familial hyperalpha-lipoproteinemia. Metabolism, *26:* 469 (1977).
7. Nichols, A. V.: Human serum lipoproteins and their relationships. Advan. Biol. Med. Phys., *11:* 109 (1967).
8. Nikkila, E.: Studies on lipid-protein relationships in normal and pathological sera and effect of heparin on serum lipoproteins. Scand. J. Clin. Lab. Invest. Suppl. 5: 1 (1953).
9. Rhoads, G. C., Gulbrandsen, C. L., and Kagan, A.: Serum lipoproteins and coronary heart disease in a population survey of Hawaii-Japanese men. New Engl. J. Med., *294:* 293 (1976).
10. Snedecor, G. W., and Cochran, W. G.: Statistical Methods, Ed. 6, p. 59 (Iowa State College Press, Ames, Iowa, 1967).
11. Snedecor, G. W., and Cochran, W. G.: Statistical Methods, Ed. 6, p. 135 (Iowa State College Press, Ames, Iowa, 1967).
12. Srinivasan, S. R., Frerichs, R. R., Webber, L. S., and Berenson, G. S.: Serum lipoprotein profile in children from a biracial community. Circulation, *54:* 309 (1976).
13. Tsang, R. C., Fallat, R. W., and Glueck, C. J.: Cholesterol at birth and age 1: Comparison of normal and hypercholesterolemic neonates. Pediatrics, *53:* 458 (1974).
14. Tsang, R. C., and Glueck, C. J.: Perinatal cholesterol metabolism. In: L. A. Barness, and R. M. Pitkin: Clinics in Perinatology, Vol. 2, No. 2, pp. 275–295 (W. B. Saunders Co., Philadelphia, 1975).
15. Tsang, R., Glueck, C. J., Evans, G., and Steiner, P. M.: Cord blood hypertriglyceridemia. Amer. J. Dis. Child., *127:* 78 (1974).
16. Tsang, R. C., Glueck, C. J., Fallat, R. W., and Mellies, M. J.: Neonatal familial hypercholesterolemia. Amer. J. Dis. Child., *129:* 83 (1975).

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Extrauterine life gestational age glomerular filtration rate inulin clearance

Glomerular Filtration Rate during the Period of Adaptation to Extrauterine Life

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Summary

Inulin clearance (C_{in}) was measured in 20 infants of 27–43 weeks of gestation during the first 24 hr of their extrauterine life. C_{in} ranged from 0.7–4.7 ml/min and correlated with gestational age ($P < 0.05$). In 18 infants of similar gestational ages studied after 2–3 days of extrauterine adaptation, the C_{in} ranged from 1.1–17.9 ml/min and also correlated with gestational age ($P < 0.01$). By day 2–3, the infants of near term gestational age achieved a greater increase in C_{in} than did the markedly preterm infants, as reflected by a significantly different slope of the regression line for C_{in} and gestational age for the infants studied at 1 vs. 2–3 days of age ($P < 0.001$).