Chapter 2

LIPOPROTEIN METABOLISM IN PREGNANCY

**Robert H. Knopp, Bartolomé Bonet, Miguel Angel Lasunción,
Adela Montelongo and Emilio Herrera**

TABLE OF CONTENTS

I. INTRODUCTION

Alterations in the metabolism of cholesterol and triglyceride and in the lipoprotein cascade are most commonly associated with the atherogenic process and the occurrence of coronary artery disease, peripheral vascular disease, and stroke. On the other hand, the lipoprotein transport system subserves essential bodily functions and, in connection with reproduction, lipoprotein metabolism is crucially associated with oogenesis, changes in the menstrual cycle, responses to sex steroid hormones, and probably its most complex expression, pregnancy itself where the function of every physiological system is altered.[1] In turn, abnormalities in lipoprotein metabolism could be related to abnormalities in reproductive function.

The purpose of this review is to consider the alterations occurring in lipoprotein metabolism in human pregnancy and in selected animal models and to attempt to understand the reasons for these changes and the possible significance for maternal physiology and fetal growth and development. The effects of diabetes mellitus on the system will be briefly considered.

II. BASIC MECHANISMS OF SEX HORMONE EFFECTS ON LIPOPROTEIN METABOLISM

The effect of estrogen on lipoprotein metabolism has been extensively studied and recently reviewed.[2-5] As shown in Figure 1, cholesterol enters the circulation from the diet incorporated as a minor component in the triglyceride-rich chylomicron. Lipoprotein lipase (LPL) removes the triglyceride from these chylomicrons upon contact with this capillary endothelium-bound enzyme. Free fatty acids (FFA) released from the hydrolytic activity of LPL are transported in the circulation bound to albumin or transferred directly through the capillary endothelium to underlying tissues for subsequent metabolism. Several studies have suggested that lipoprotein lipase activity might be either slightly reduced or unchanged in the presence of estrogen alone.[6,7] This reduction, although not always consistent and possibly minor, may contribute to the hypertriglyceridemia associated with estrogen administration (see below). As indicated in Figure 1, the relatively cholesterol-rich metabolic product of lipoprotein lipase action, the chylomicron remnant, may have enhanced uptake by the hepatic receptor, known as the LDL related protein (LRP) and designated in the illustration as E. The receptor resembles the low density lipoprotein (LDL) receptor but it is specific for recognition and uptake of lipoproteins carrying multiple copies of apolipoprotein E.[8,9] Studies from oral contraceptive-treated individuals where chylomicron remnants were labeled with retinyl palmitate indicate an enhanced rate of uptake.[10] This effect may be estrogen rather than progestin dependent because the LRP resembles the LDL receptor which is upregulated by estrogen (see below).

Once cholesterol reaches the hepatic pool and mixes, presumably, with endogenously formed cholesterol in the liver, it is resecreted in the form of
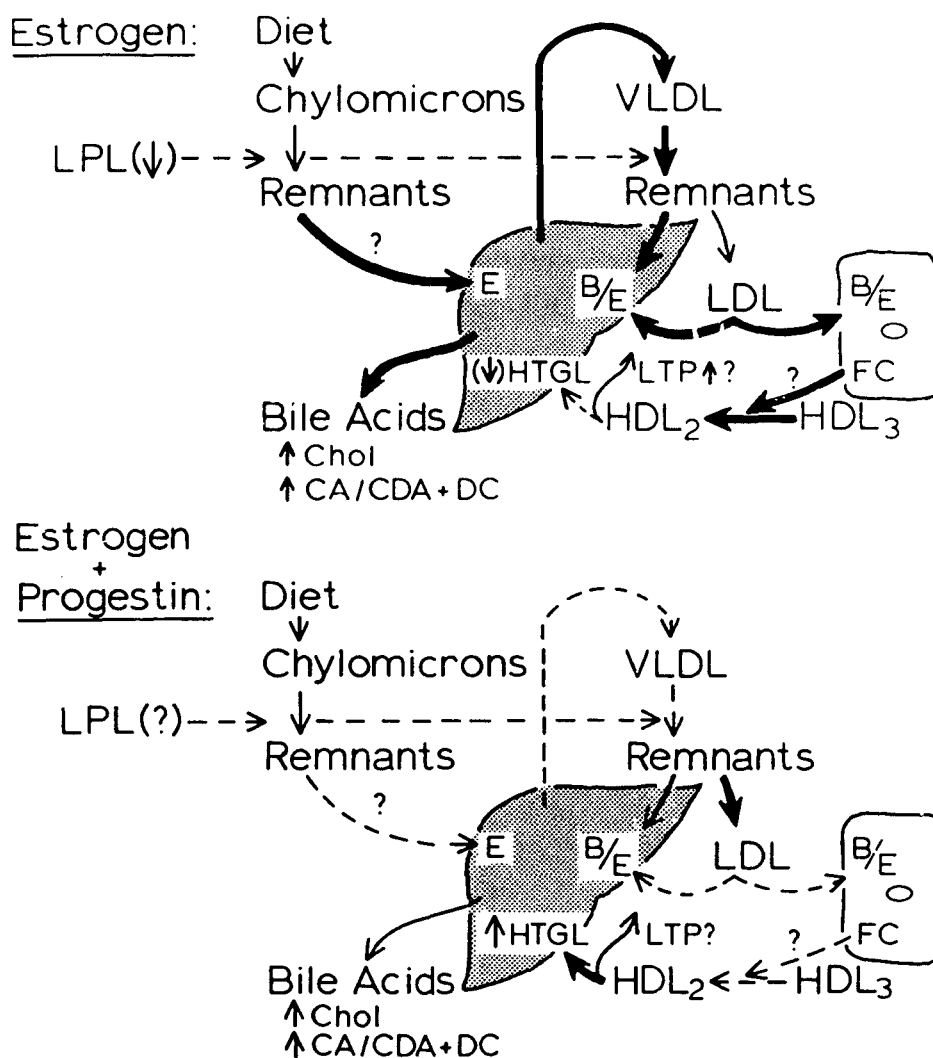
FIGURE 1. Transport of lipid via the lipoprotein cascade. Broad, dark lines indicate an increased rate of transport. A dashed line indicates diminished transport. A ? indicates uncertainty about the rate of transport of a given pathway. Other abbreviations are indicated in the text. (From Knopp, R. H., in *Oral Contraception into the 1990's*. Parthenon Publishing, Park Ridge, NJ, 1989. With permission.)

endogenous triglyceride-rich very low density lipoprotein or VLDL (Figure 1). This process is increased by estrogen.[11] The triglyceride of this lipoprotein is similarly degraded in extrahepatic tissues by interaction with capillary endothelium bound LPL. FFA are again formed, although the rate of their generation is much less rapid (and the clearance of VLDL slower) than from chylomicrons. As shown in the figure, VLDL remnants are formed similar to the chylomicron remnant, but the fate of the VLDL remnant is different. VLDL remnants can be removed directly by the liver or can be subsequently degraded with further triglyceride removal via transfer to high density lipoprotein (HDL) in exchange for HDL esterified cholesterol mediated by the lipid transfer protein (LTP) or by the action of hepatic triglyceride lipase (HTGL) that is similar but not identical to LPL. With the further removal of triglyceride, LDL forms and then is amenable to removal by the LDL receptor. Hepatic uptake of VLDL remnants and removal of LDL are mediated by the LDL receptor, designated the B/E receptor in the illustration. In the case of

the remnant, it is believed that apoprotein E is the signal for uptake and in the case of LDL it is apoprotein B, but in both instances the same receptor is responding to the apoprotein on the surface of the lipoprotein particle. The important point is that estrogen upregulates the LDL receptors[12,13] which then enhances the clearance of VLDL remnants and LDL-cholesterol (LDL-C). Thus, with estrogen therapy in humans, remnant clearance is enhanced[14] and subjects with an abnormal accumulation of remnants as in type III hyperlipidemia improve with estrogen therapy.[15] Given in pharmacological amounts in the rodent, estrogen can induce the near disappearance of LDL due to such an exaggerated upregulation of the LDL receptor.[16]

The sites where estrogen alters HDL-mediated reverse cholesterol transport are not completely understood. A receptor-mediated mechanism for the association of the most cholesterol-poor of the HDL species, HDL_3, which is also apoprotein A-II as well as apo A-I rich, exists[17] but its response to estrogen is unknown. Activation of this receptor stimulates translocation of cholesterol from intracellular pools to the surface where HDL acquires the cholesterol on a concentration gradient.[17] The well-established effect of estrogen is to increase the plasma concentration of the more cholesterol-rich form of HDL_2 which may relate to an increased synthesis of apoprotein A-I[11] as well as possibly to a diminished removal.[18] An increase in the content of HDL_2-Cholesterol (C) is related to an estrogen-induced reduction in HTGL activity[19] which reduces the hydrolysis of HDL-phospholipid[20] and the resulting concentration-dependent transfer of cholesterol to the liver.[20] The increase in plasma HDL cholesterol (HDL-C) concentration should favor cholesterol transfer to VLDL and LDL via LTP, leading to the final clearance of cholesterol via the hepatic LDL receptor and the bile acid pathway.[21] As mentioned above, triglycerides from VLDL are transferred to HDL in exchange for HDL esterified cholesterol. This transfer seems to be the mechanism by which exogenous estrogens increase HDL-triglyceride (HDL-TG) levels.[22] LTP may be increased by estrogen like other hepatic proteins since McPherson et al. have found that LTP concentrations in plasma are 25% higher in women than in men.[21] Finally, bile acid excretion is increased as is cholesterol excretion (Figure 1). In summary, as indicated then in Figure 1, the effect of estrogen is to enhance most and possibly all of the pathways of lipoprotein transport.

The effect of progestins is to oppose most effects of estrogen either by acting as an anti-estrogen directly or by exerting its own effect on lipoprotein metabolism. At present it is impossible to say if the anti-estrogen effects of progestins are related to a progestational effect of the progestin or an androgenic effect of progestins that varies depending on the chemical structure of the progestin. However, even natural progesterone when given in combination with estrogen will oppose the lipoprotein effects induced by estrogen.[2-4,23] Unfortunately, the data to document the general effect of progestins on lipoprotein metabolism is fragmentary and in some cases conflicting. In the case of intestinal fatty acid or cholesterol absorption, no information is

available to our knowledge. With respect to the uptake of remnants, the cholesterol content of VLDL increases relative to triglyceride in subjects taking androgenic, progestin-dominant oral contraceptives, suggesting an impaired removal of remnants.[24] On the otherhand, studies in progestin-treated rodents indicate that an increase in remnant uptake might be induced.[25] The question has not been systematically studied in humans. Plasma triglyceride concentrations tend to fall with progestin administration or with progestin dominant oral contraceptives,[24] and hepatic secretion rates in animal models are reduced.[26,27] LDL clearance appears to be reduced, again in rodents[25] given an androgenic progestin and HDL-C concentrations fall.[2-4,24] This effect could be due in part to an androgen/progestin mediated upregulation of hepatic lipase activity which increases the removal of HDL-C from the circulation.[2-4,19] Effects of progestins on bile acid metabolism are not well investigated.

The above pharmacologic effects of sex hormones can be seen when lipoproteins are compared in women vs. men.[2] In health, premenopausal women have lower plasma triglyceride, lower LDL-C levels, higher HDL-C levels, and a more rapid rate of plasma triglyceride clearance than do men. Even in disease states such as diabetes, female responses differ from (and are greater than) men.[28] It appears that all of these effects can be attributed to the effect of estrogen. In general, whether one is considering the normal menstrual cycle or postmenopausal estrogen therapy, C-21 progestins or natural progesterone have little antagonistic effect on LDL.[19,29,30] Thus, in normal female physiology, estrogen effects dominate over natural progesterone effects and as will be seen, this generalization applies to pregnancy as well.

III. LIPOPROTEIN ALTERATIONS IN PREGNANCY

Lipoprotein changes in pregnancy have been studied in several centers in humans[31-37] (see Reference 38 for review of extensive earlier literature prior to 1978). As shown in Figure 2, plasma total triglyceride and cholesterol increase 250% and about 25% respectively. A linear increase in triglyceride rapidly declines postpartum and while a more asymptotic increase in cholesterol[31] declines more slowly postpartum.[32] Examining Figure 3, it can be seen that the cholesterol increase is primarily in the LDL which increases from 100 to 160 mg/dl or approximately 60% while the VLDL-cholesterol (VLDL-C) increase is small. A contrasting biphasic pattern is seen in HDL-C where a maximum rise is seen by 20 weeks gestation and then a gradual decline by 39 weeks gestation to a value of approximately 64 mg/dl, approximately 10 mg/dl higher than the nonpregnant HDL-C value of 55 mg/dl. Thus although a shifting HDL pattern is seen in pregnancy, the HDL-C remains elevated throughout.[31,32]

Plasma triglyceride concentrations in the lipoprotein fractions are shown in Figure 4 and Table 1 and indicate that the greatest triglyceride increase is seen in VLDL but nearly as great an increase is seen in LDL as well; the
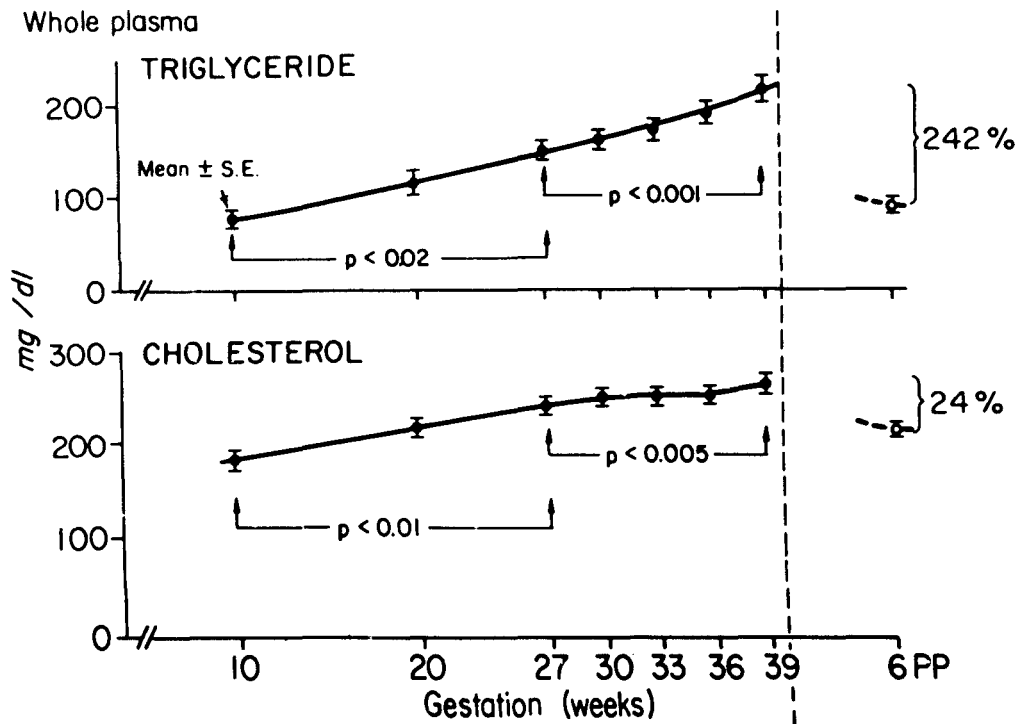
FIGURE 2.   Increases in plasma triglyceride and cholesterol concentrations in 8 to 20 subjects studied serially throughout gestation. Eight subjects were studied throughout the entire gestation and an additional 12 subjects (for a total of 20) were studied between weeks 27 and 39. Tests of significance of increases at gestational intervals are as shown. (From Knopp, R. H., Warth, M. R., Charles, D., Childs, M., Li, J. R., Mabuchi, H., and Van Allen, M., *Biol. Neonate (Paris)*, 50, 297, 1986. With permission of S. Karger AG, Basel.)

triglyceride content increases in all the fractions to a greater extent than cholesterol. Even in HDL, triglyceride concentrations increase approximately 25% and are sustained in contrast to the late gestation decline in cholesterol in the HDL particles at late gestation. The ratios of cholesterol/triglyceride in the lipoprotein fractions are described elsewhere.[33] The increase in HDL-C is seen primarily in HDL_2 as shown in Figure 5 whereas relatively little increase is seen in HDL_3.[32]

Apolipoprotein changes in pregnancy have also been reported in several investigations[32,35,39–44] (see late gestation examples in Table 1). Total plasma apoprotein-B increases throughout gestation and is associated with the total cholesterol concentration.[40,41] An apo-B increase is found in the VLDL fraction at 36 weeks where the increase is about threefold and in the LDL concentration where the increase is about 40% (see Table 1).[39] The increase in apoprotein A-I, the major apolipoprotein of HDL is ~28%.[39,41,42] Lp(a) has been measured in one study of normal pregnancy,[43] increasing about 100% by week 20 of gestation and then declining towards normal at term. Serial measurements of apoproteins A-I and A-II (Figure 6) show that the apoprotein A-I increase is sustained throughout gestation unlike the HDL-C rise and fall. A similar finding has been observed by Desoye et al.[35] and Rosing et al.[42] Nonetheless, as shown in Figure 7, a highly significant linear correlation exists between plasma apoprotein A-I and HDL-C among individual values
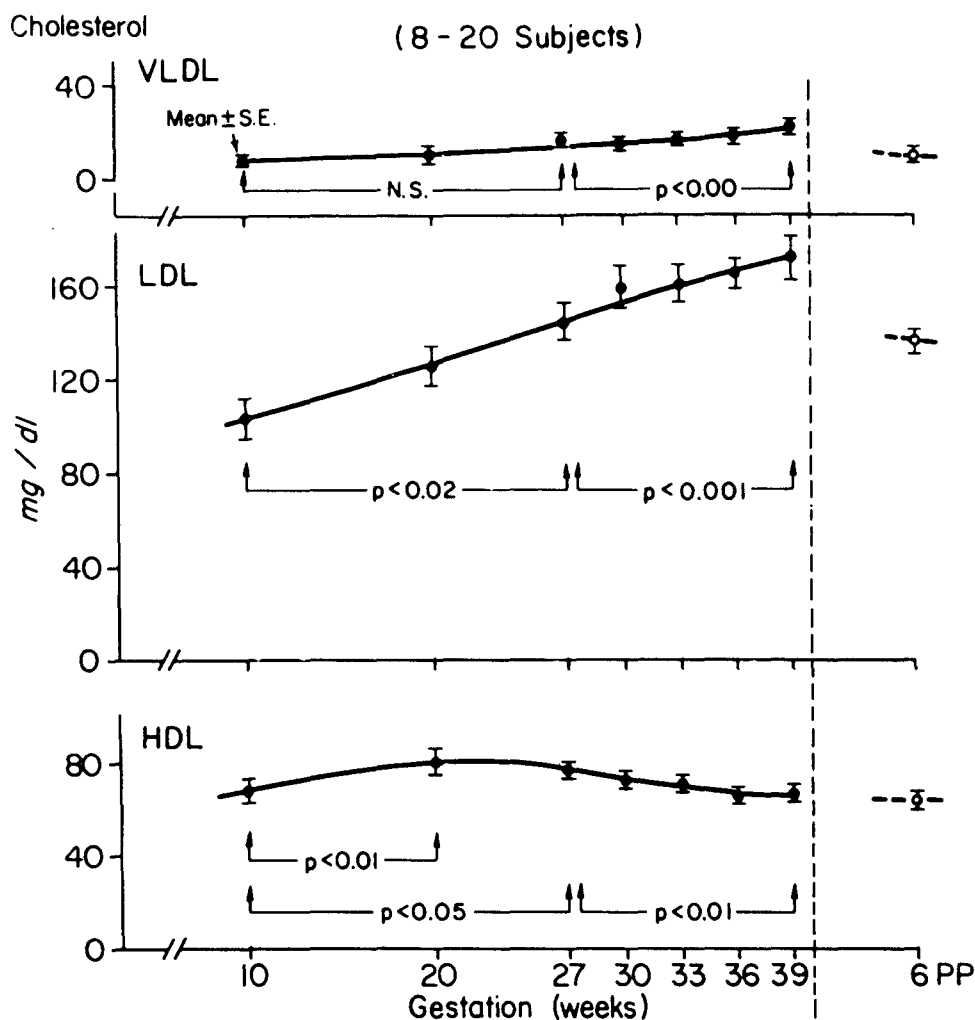
FIGURE 3. Changes in lipoprotein cholesterol concentrations in the same 8 to 20 subjects described in Figure 2. VLDL and LDL concentrations show increases throughout gestation, whereas HDL-C concentrations show a statistically significant rise between 10 and 20 weeks, and 10 and 27 weeks, but a significant fall between 27- and 39-weeks gestation. Notice that the LDL-C concentration has not returned to the gestational week-10 level at 6-weeks postpartum. (From Knopp, R. H., Montes, A., Childs, M., Li, J. R., and Mabuchi, H., *Clin. Obstet. Gynecol.*, 24, 21, 1981. With permission.)

from a three trimester and postpartum longitudinal study in 32 women (Montelongo, A., Herrera, E., and Lasunción, M. A., previously unpublished data). With regard to apoprotein A-II, neither we[2] nor Rosing et al.[42] found an increase (Figure 6)[2] while Desoye et al. observed a significant increase in apoprotein A-II of 20%.[35]

Reference values for lipoprotein lipid concentrations at 36-weeks gestation have been reported.[44] These values are presented in Table 2. Because lipoprotein lipid measurements in pregnancy[44] were obtained in the same standardized laboratory that determined reference values for the nonpregnancy age population, extrapolations can be made for the 10th to 90th percentiles throughout the period of gestation based on the reference values of nonpregnant subjects[45] and the change in the mean triglyceride and cholesterol concentrations through gestation[31,32] and shown in Figure 2. These

Triglyceride   (8 - 20 Subjects)

80   VLDL

Mean ± S.E.

40   p<0.01

0 —//——   p<0.05

80   LDL

mg / dl

40   p<0.001

0 —//——   p< 0.001

HDL

40

0 —//——   p<0.001   N. S.

—//——
        10   20   27 30 33 36 39   6 PP
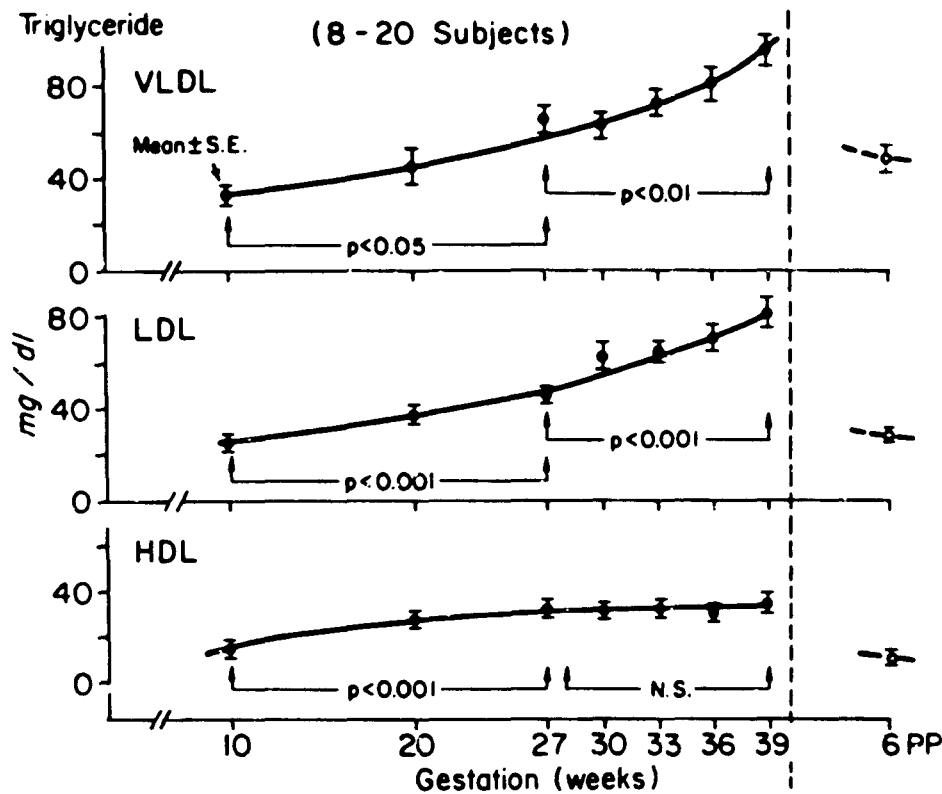   Gestation (weeks)

FIGURE 4.   Increases in lipoprotein triglyceride concentrations throughout gestation. Subjects are the same as shown in Figures 2 and 3. Statistically significant increases in VLDL and LDL triglyceride concentrations during the first and second halves of gestation are shown. A significant increase in HDL triglyceride is seen only in the interval between 10 and 27 weeks. (From Knopp, R. H., Montes, A., Childs, M., Li, J. R., and Mabuchi, H., *Clin. Obstet. Gynecol.*, 24, 21, 1981. With permission.)

extrapolations are shown in Figure 8 and can be used to interpret the extent of lipid elevation at any time throughout pregnancy.

In summary, the changes in lipoprotein lipids in pregnancy disclose increases in each fraction although HDL-C declines somewhat in the second half of gestation from a midgestation peak. Thus, different mechanisms must control concentrations of the lipoprotein fractions in pregnancy. For instance the VLDL, LDL, HDL, and apoprotein rises including Lp(a) in the first half of pregnancy may be sex-hormone dependent while the contra-insulin hormones of late gestation may drive VLDL and LDL higher while depressing HDL and opposing a further hormone dependent rise in apo A-I and a decline in Lp(a).

Lipoprotein lipid changes with gestation in animal models vary greatly with species. An exhaustive comparison of these changes is not possible in this review but it can be said that plasma VLDL triglyceride concentrations in the rodent increase similarly to that in the human.[46,47] On the other hand, in the rhesus monkey, plasma triglycerides decline and then rise, but cholesterol and LDL-C and HDL-C concentrations fall throughout gestation.[48-50] In the rat, HDL-C does not increase while LDL-C increases slightly, but LDL levels remain much lower than in humans.[46,47] Thus, even qualitative

TABLE 1
Comparison of Lipoprotein Lipid and Apoprotein Concentrations (mg/dl; Mean ± SD) in 36-Week Gestation Pregnancy Compared to Nonpregnant Control Subjects

	Nonpregnant	36-Week gestation
Total	(23)[a]	(23)[a]
Triglyceride	59 ± 19	222 ± 60
Cholesterol	171 ± 26	251 ± 32
VLDL		
Triglyceride	33 ± 14	107 ± 41
Cholesterol	11 ± 6	22 ± 9
Apo B	7 ± 6	20 ± 11
LDL		
Triglyceride	14 ± 10	72 ± 21
Cholesterol	104 ± 23	161 ± 39
Apo B	61 ± 10	84 ± 23
HDL		
Triglyceride	12 ± 6	29 ± 9
Cholesterol	56 ± 12	64 ± 9
Apo A-1	128 ± 23	164 ± 16
HDL_2	(19)	(18)
Cholesterol	22 ± 8	38 ± 12
HDL_3		
Cholesterol	34 ± 5	31 ± 6

Note: All data taken from Montes et al.[39] except those of HDL_2 and HDL_3 which are from Fähraeus et al.[34]

[a] Number of subjects denoted in parentheses.

From Knopp, R. H., Warth, M. R., Charles, D., Childs, M., Li, J. R., Mabuchi, H., and Van Allen, M., *Biol. Neonate (Paris),* 50, 297, 1986. With permission of S. Karger AG, Basel.

extrapolations from animal models to humans are limited and must be species and lipoprotein-fraction specific to be interpretable.

IV. PHYSIOLOGIC MECHANISMS AFFECTING LIPOPROTEIN METABOLISM IN PREGNANCY

Fat absorption in human pregnancy has not been studied to our knowledge. While absorption of triglyceride and fatty acids in the gut is quantitative in humans, the absorption of cholesterol is limited to about 30 to 50% of fat ingested. Thus, it is possible that there might be an increase in cholesterol absorption. Argiles and Herrera[51] have found that the appearance of labeled lipids in d < 1.006 lipoproteins in plasma after an oral radioactive triglyceride load is enhanced in the pregnant rat as compared to nonpregnant controls.
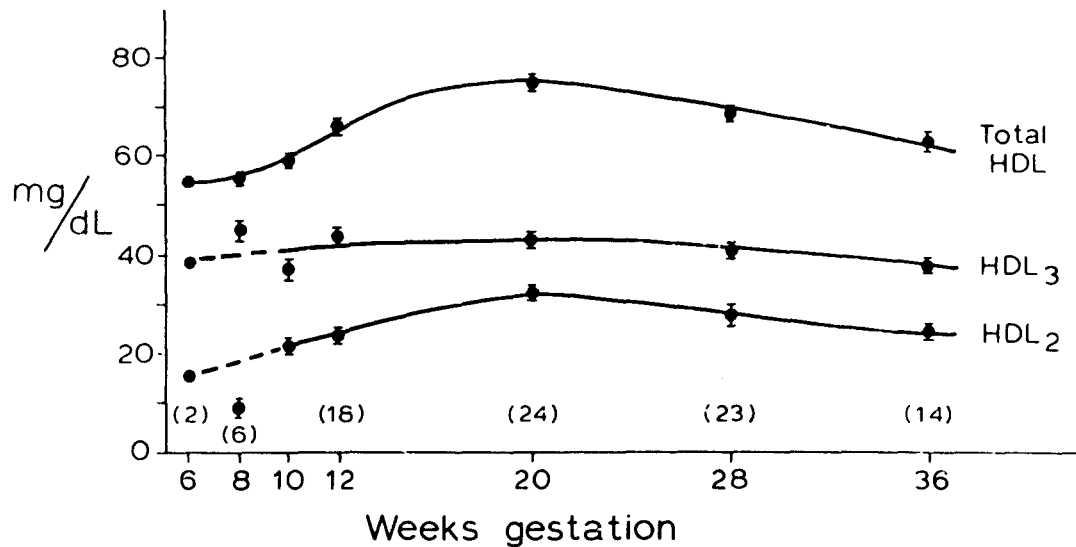
FIGURE 5. Changes in HDL-C subfractions during pregnancy. The increase and decline in total HDL-C concentrations are taken from the second series of pregnant subjects (the numbers are shown in parentheses at the bottom of the illustration) and confirm the HDL changes described in Figure 3. HDL_2 and HDL_3 subfractions are examined. A major increase is seen in HDL_2-C. (From Knopp et al., *Principles of Perinatal-Neonatal Metabolism*, Cowett, R. M., Ed., Springer-Verlag, New York, 1991, 177. With permission.)
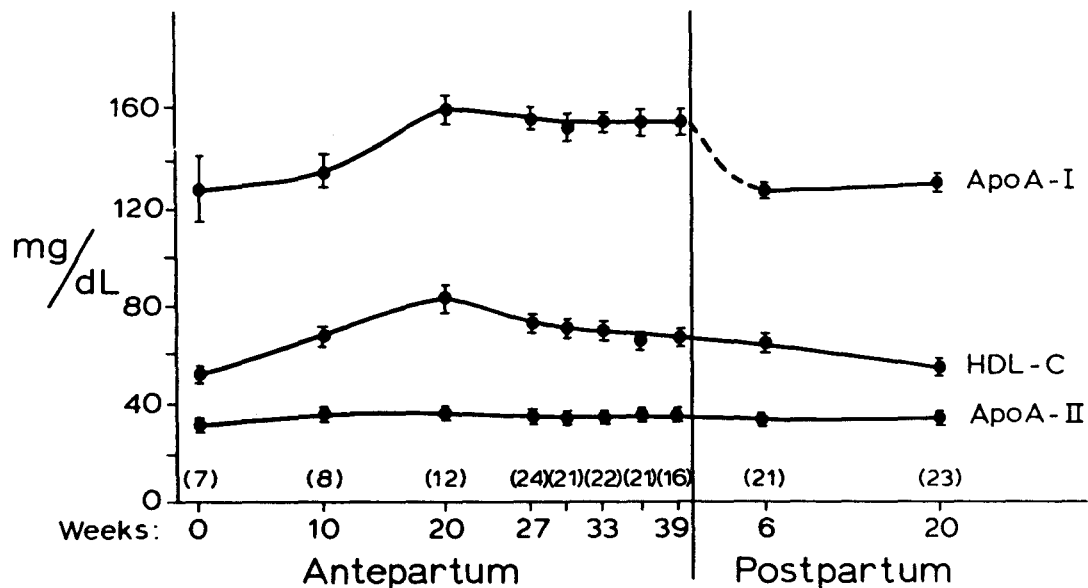

FIGURE 6. HDL-C and apoprotein concentrations in pregnancy. The HDL-C concentrations shown here are from the same subjects that appear in Figure 5. Apoprotein A-II concentrations show a parallel rise up to 20-weeks gestation and then show no further change in contrast to the drop in HDL-C concentrations between weeks-20 and -39 gestation. Apoprotein A-II concentrations show no change. (From Knopp et al., *Principles of Perinatal-Neonatal Metabolism*, Cowett, R. M., Ed., Springer-Verlag, New York, 1991, 177. With permission.)

Since the overall disposition of labeled lipid was not enhanced, it is concluded that intestinal triglyceride absorption is increased in rat pregnancy. The production of VLDL protein has been studied in pregnant rat and has been found
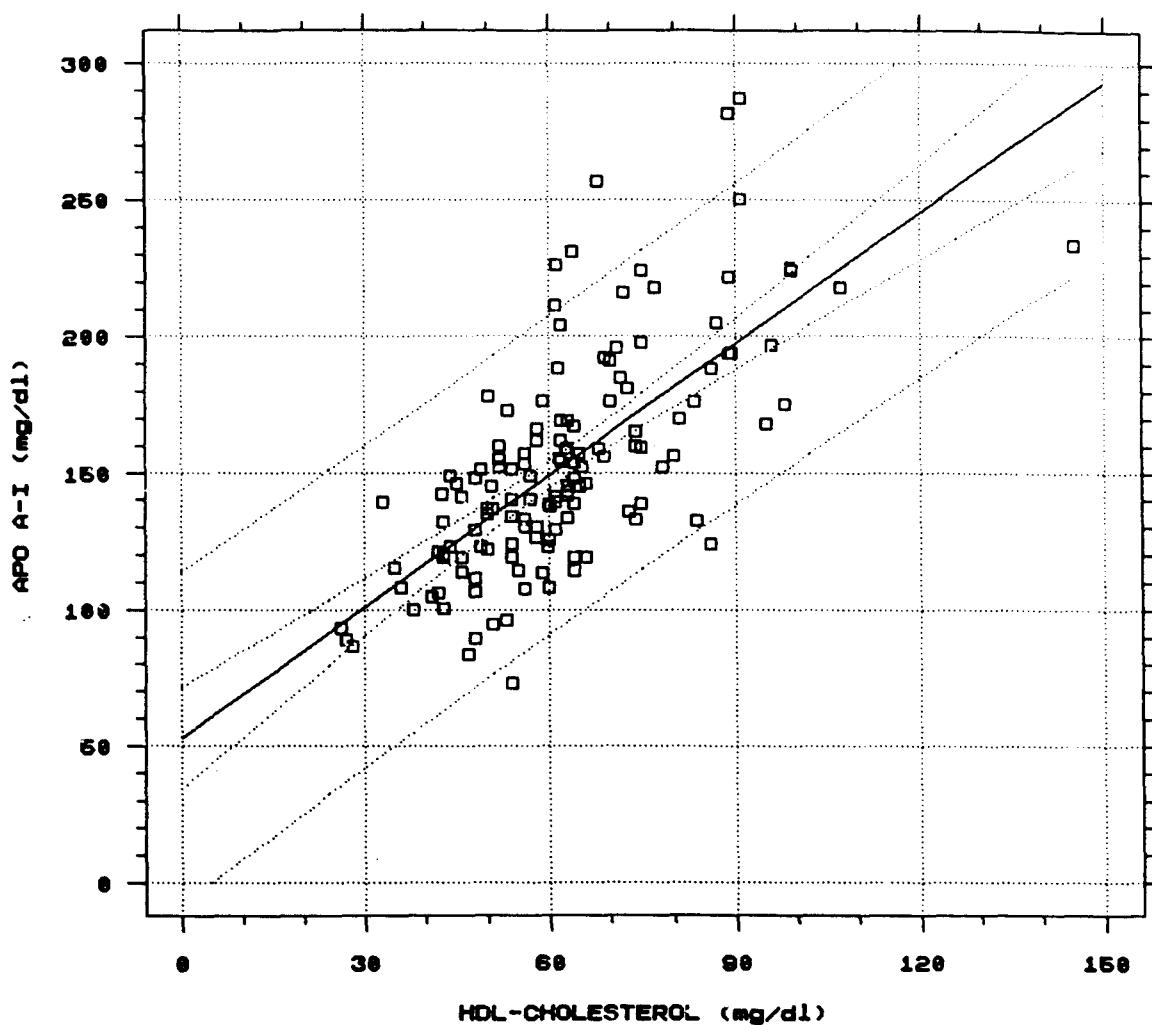
FIGURE 7. Correlation of apoprotein A-I and HDL-C concentrations in pregnant women in the three trimesters of pregnancy and postpartum. A statistically positive association is seen (R = 0.689) less than 0.001 in 135 subjects. (Previously unpublished results of Montelongo, A., Herrera, E., and Lasunción, M. A.)

to be increased in several investigations. Using the triton method to block triglyceride removal from the circulation via the lipoprotein lipase reaction, plasma triglyceride concentration increased two or threefold in pregnancy.[32] In a separate study in pregnant rats, the clearance of d < 1.019 triglycerides from the circulation employing radiolabeled chylomicrons followed the same exponential curve vs. concentration as nonpregnant animals indicating that increases in triglyceride concentration are related less to differences in removal than production.[52] Triglyceride secretion in the perfused liver has also been observed to be increased.[53] The influences of fat vs. high carbohydrate feeding in the pregnant rat have also been studied.[54] With high carbohydrate feeding, the expected "carbohydrate induction" is seen with an increase in VLDL lipoprotein triglyceride concentrations, although this effect is less than expected in high carbohydrate fed pregnant women.[55] On the other hand, upon cessation of fat feeding, the clearance of chylomicron triglyceride from the circulation is slower in the pregnant rat than in the nonpregnant rat, as might be expected if VLDL levels are elevated and compete with chylomicrons for

TABLE 2

Plasma Triglyceride, Cholesterol, and Lipoprotein Cholesterol Distributions in 553 Randomly Selected Women at 36-Weeks Gestation

| | Percentiles | | | | |
	5th	10th	50th	90th	95th
Triglyceride	133[a]	146	209	341	387
Cholesterol					
Total	185	196	243	299	318
VLDL	8	12	26	47	59
LDL	89	106	148	200	218
HDL	42	46	64	86	93

[a] Results are presented in mg/dl. Reproduced in part from Reference 44.

removal by LPL. In other words, the disappearance of triglyceride from the plasma seems to be impaired in these rodent studies but could be entirely explained by increased hepatic triglyceride production and an increased plasma triglyceride pool size. It may be concluded from these studies that the production of triglyceride-rich lipoproteins is enhanced in the late pregnant rat and that this action seems to be the major contribution in the development of maternal hypertriglyceridemia.

The extent to which diminished LPL activity in various tissues in the body contribute additionally to the hypertriglyceridemia is uncertain. What is clear is that LPL activity is reduced markedly in adipose tissue,[36,54,56–59] becomes progressively higher in the mammary gland,[36,56–59] and is present in the placenta[32,36,58,60,63] with increasing activity near parturition.[36,58] Thus the reduction in adipose tissue LPL may serve to divert plasma triglyceride fatty acids to tissues with remaining LPL activity such as the uterus,[59] the placenta (the activity of which seems unaffected by diabetes),[32] muscle tissue, and the mammary gland. On the other hand, total postheparin lipolytic activity (PHLA) measured as LPL is reduced in human pregnancy by 85%, far beyond the effect of LPL dilution in the larger plasma volume of pregnancy.[36] PHLA is reduced to a lesser extent in rodents.[61] When VLDL-triglyceride (VLDL-TG) values of women at different times of gestation and postpartum are plotted against the plasma LPL activity measured 10 min after 50 IV of heparin/kg administered intravenously, a significant inverse correlation is seen (Figure 9) (Montelongo, A., Herrera, E., and Lasunción, M. A., previously unpublished data). Thus, LPL-mediated TG removal may be impaired, further contributing to the elevated triglyceride concentration. The placental transfer of triglyceride fatty acids and the role of placental LPL is discussed below.
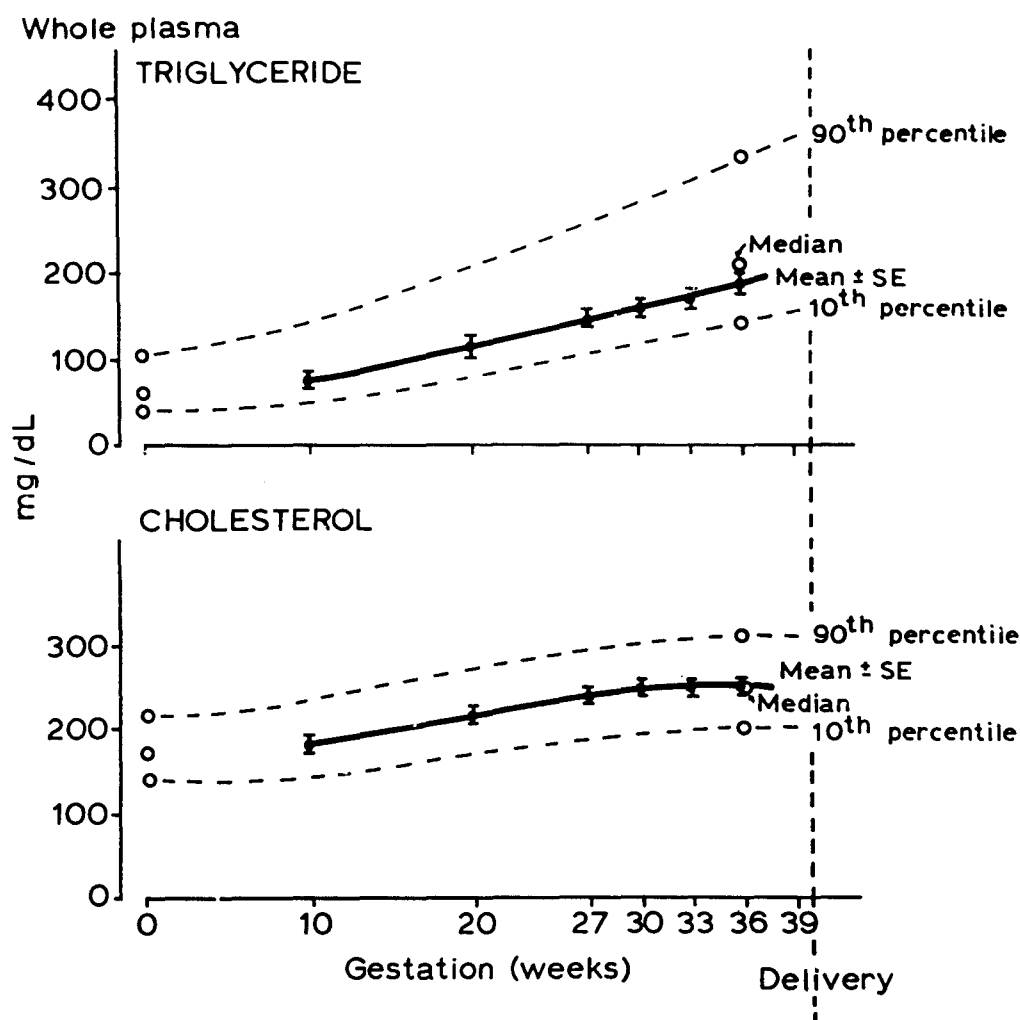
FIGURE 8. Tenth to ninetieth percentile confidence intervals around the rise in total plasma triglyceride and cholesterol concentrations throughout gestation based on population-based surveys of total cholesterol and triglyceride concentrations in nonpregnant women (week 0) and pregnant women at 36-weeks gestation (based on References 44 and 45).

Regardless of the relative extent of triglyceride over-production vs. under-removal, the high concentration of endogenous triglyceride-rich lipoproteins (VLDL) along with chylomicron triglyceride fatty acids should enhance fatty acid transport to the fetus since placental LPL activity rises as term approaches.[36,58] This schema is consistent with a diversion of ingested nutrients from maternal fat tissue to muscle and from the fetus to meet energy and growth requirements, respectively (see Reference 31 and other chapters in this book for review of alterations in other fuels). The result is that adipose tissue mass which is the major source of endogenous fatty acid declines at some time in late gestation (see Chapter 1 in this book) although the exact time varies among laboratories, strain of rat,[36,61] and even location of fat deposit.[62]

The clearance of remnants and low density lipoprotein in pregnancy has been little studied. In the feeding experiments in pregnant rats referred to above, trends toward increased percent cholesterol content of VLDL were noted, ranging from 15 to 60%.[55] In human pregnancy the density of 1.006 to 1.019 fraction lipoproteins (intermediate density lipoprotein or IDL) was
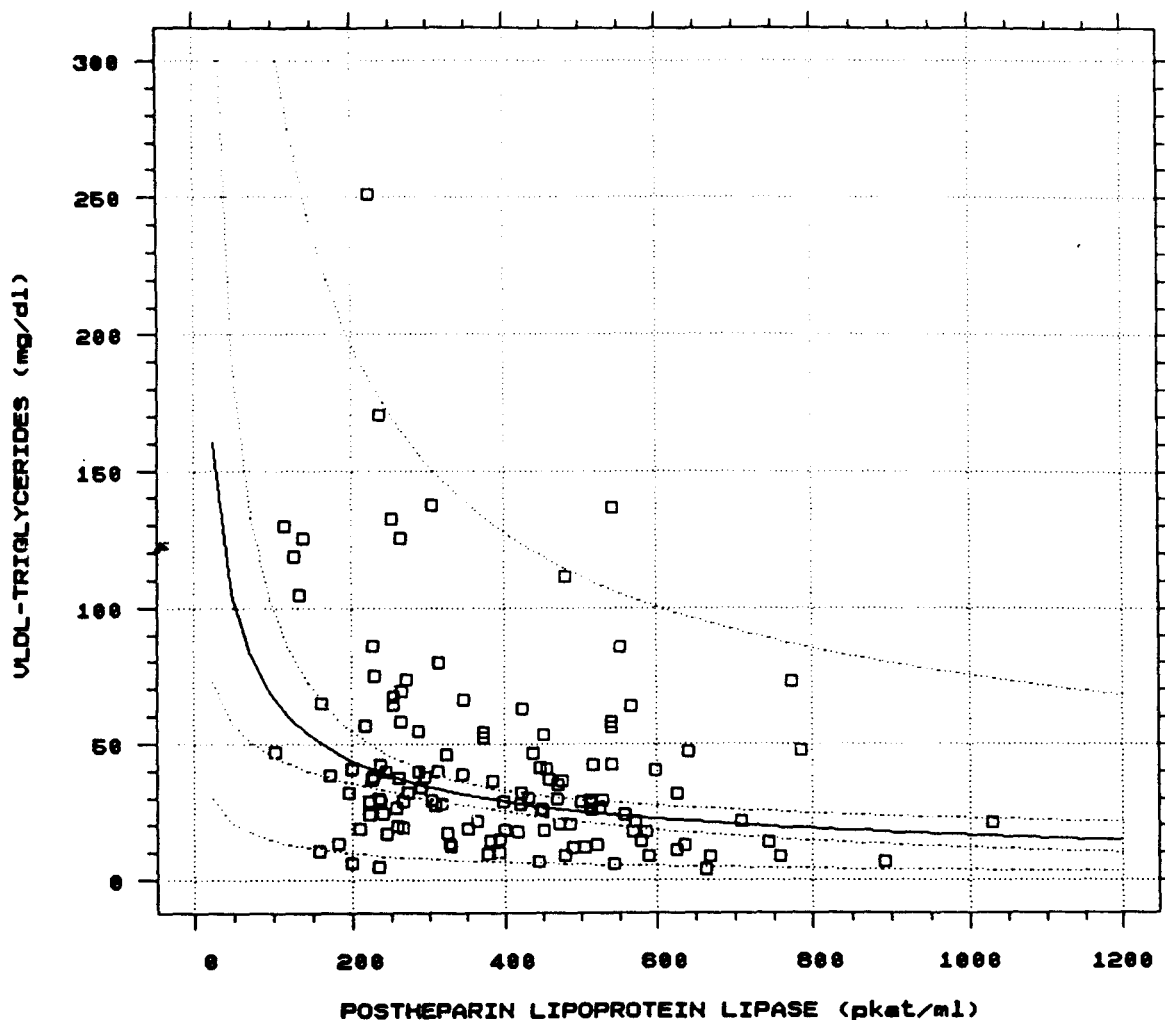
FIGURE 9. The association (multiplicative regression) between VLDL-triglyceride concentrations and postheparin lipoprotein lipase activity in plasma. The association is -0.350 ($p <$ 0.001) in 126 subjects. A curvilinear inverse relationship is shown between the two parameters. Data are from 126 observations in women who were pregnant in the first, second, and third trimesters and postpartum. (Previously unpublished results of Montelongo, A., Herrera, E., and Lasunción, M. A.)

increased but resembled the increases in VLDL and LDL.[64] Beta migrating VLDL was seen in 1.1% of 36-week-pregnant women and 1.6% of 6-week-postpartum women, though there were no cases in 179 nonpregnant women.[44] Thus, at the worst, the accumulation of remnants in pregnancy seems in proportion to the increase in the other lipoprotein fractions.

With respect to LDL-C metabolism in pregnancy, the matter has been studied twice in animal models with conflicting results. In WHHL rabbits, LDL was cleared more rapidly in pregnancy than in the nonpregnant state suggesting increased nonreceptor mediated clearance mechanisms with no reduction in VLDL input.[65] On the other hand, LDL receptor mediated clearance by the liver and whole animal in pregnancy using radiolabled LDL was reduced in rat pregnancy as was nonreceptor mediated clearance.[66] The reduction in hepatic clearance of LDL in the pregnant rat might be related to increased hepatic cholesterol production in the rat which has been reported,[67]

although HMG-CoA reductase activity is reportedly not increased.[68] The subject of LDL-C metabolism has been even less studied in pregnant women. In a woman with heterozygous-familial hypercholesterolemia, pregnancy caused dramatic reductions of serum cholesterol and LDL-C levels, and this effect was interpreted to be the result of estrogens increasing LDL-C removal through LDL-receptors.[69] This effect is paradoxical of course, to the extent that LDL-C usually rises in pregnancy (see foregoing discussion). If LDL clearance is increased as a result of estrogen action in pregnancy, LDL entry must be even greater. A defect in LDL entry could operate in this unusual case.[69]

The extent to which the elevations in HDL and apoprotein A-I are due to increased secretion as opposed to diminished removal in pregnancy is uncertain. What is known is that hepatic triglyceride lipase concentrations in pregnancy are reduced[70] and that this reduction may contribute to a rise in HDL-C and HDL-TG concentrations at least. In fact, a highly significant negative association exists between HDL-TG and post-heparin hepatic lipase when measured in plasma of normal women in the three trimesters of gestation and postpartum 10 min after i.v. administration of 50 IU of heparin/kg (Figure 10) (Montelongo, A., Herrera, E., and Lasunción, M. A., previously unpublished data). This finding indicates a close relationship between the increased HDL-TG levels seen during late gestation in women and a reduction in hepatic lipase activity that would decrease the catabolic rate of these particles. In addition, Sakuma et al. found evidence of increased HDL apoprotein secretion using a radioiodine labeled HDL turnover technique.[71] The reduction in hepatic lipase activity, which is active in removing triglyceride from IDL, LDL, and HDL, could help also to explain the increased TG content of LDL (Figure 4).[32]

V. RELATIONSHIPS BETWEEN HORMONES AND LIPOPROTEINS

In an effort to understand the relationship between circulating lipid and lipoprotein concentrations and the hormones of pregnancy, correlative associations were studied between plasma lipoprotein concentrations and plasma insulin, estradiol, estriol, progesterone, and human chorionic somatomammotropin concentrations.[32] As shown in Table 3, predicted associations were, in general, found. Plasma triglyceride concentrations were positively associated with plasma estriol concentrations and VLDL triglyceride concentrations with insulin. Surprisingly, LDL-C concentrations were significantly and inversely associated with progesterone concentration while HDL-C was positively associated with progesterone concentrations. In a time series analysis rather than a cross-sectional study like that described above, Desoye and associates found, as would be expected, positive correlations of HDL lipids with estrogen, progesterone, and placental lactogen with almost all the lipoprotein fractions and apoproteins.[35] A generally inverse association with chorionic gonadotropin (hCG) was observed, as again expected, since hCG
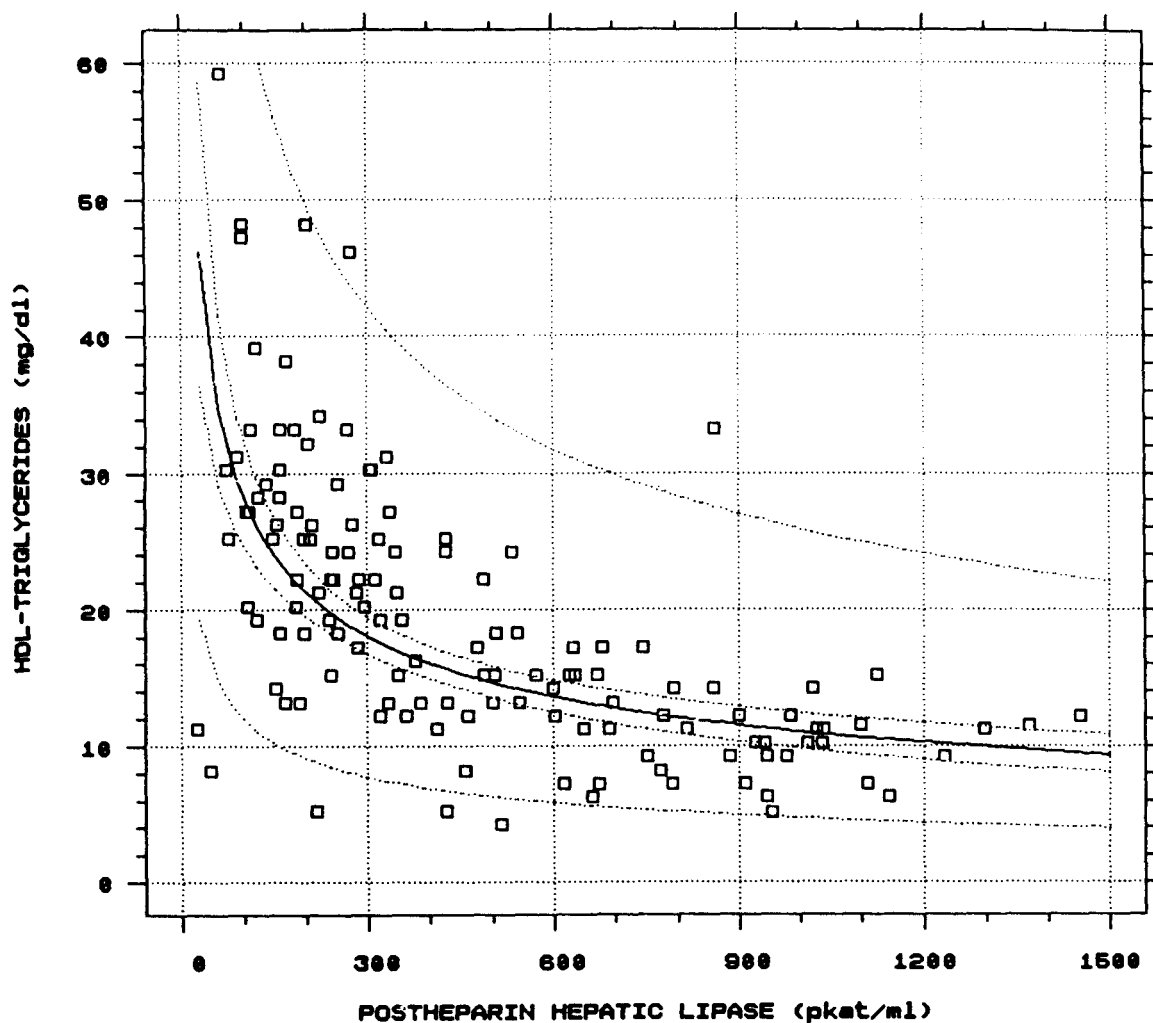
FIGURE 10. Regression of HDL triglyceride concentrations vs. postheparin hepatic lipase concentrations in 135 observations of pregnant women in the first, second, and third trimesters or postpartum (R = -0.608; $p < 0.001$). (Previously unpublished results of Montelongo, A., Herrera, E., and Lasunción, M. A.)

declines as gestation proceeds.[35] These associations do not establish causality and could reflect the utilization of lipoprotein cholesterol to make steroid hormones as much as the effect of steroids on lipoprotein metabolism (see below). Nonetheless, based on the major effects of estrogen and the minor effects of natural progesterone on lipoproteins, the lipoprotein patterns seen in pregnancy seem to reflect primarily an estrogen effect with the exception of the marked increase in LDL-C. This increase may be a result of the combined effect of high concentrations of estrogen and progestin as can be seen with oral contraceptive steroid administration.[30]

With respect to the role of insulin and insulin sensitivity, resistance to insulin occurring during late gestation seems to be responsible for the reduction in LPL activity in adipose tissue since prolonged infusion of glucose in pregnant rats increases adipose tissue LPL activity to even higher levels than in virgin animals.[72] This maneuver also reverts insulin sensitivity to normal in the late-pregnant rat.[73] Hormones are also responsible for the changes in the activity of the enzymes that drive most of these changes in

TABLE 3
Correlations of Hormone and Lipoprotein Cholesterol and Triglyceride Concentrations in Pregnancy

| | Spearman correlation coefficients | | | |
	TG	VLDL-TG	LDL-C	HDL-C
Insulin	0.09	0.14[b]	−0.09	0.00
Estradiol	0.09	0.05	0.01	0.13[a]
Estriol	0.13[a]	0.09	−0.07	0.06
Progesterone	0.04	0.02	−0.15[b]	0.15[c]
HCS[d]	0.07	0.03	--0.03	0.03

Note: Statistical significance: [a] $p < 0.05$; [b] $p < 0.02$; [c] $p < 0.01$. HCS[d] refers to placental lactogen, also known as human chorionic-somatomammotropin. After an overnight fast at 36-week gestation, 290 pregnant women were studied. See Knopp et al.[32] for descriptions of population studied and results.

From Knopp, R. H., Warth, M. R., Charles, D., Childs, M., Li, J. R., Mabuchi, H., and Van Allen, M., *Biol. Neonate (Paris)*, 50, 297, 1986. With permission of S. Karger AG, Basel.

lipoprotein metabolism in pregnancy. Thus, where estrogens are implicated in the reduction in hepatic lipase activity,[2,19] insulin also can have an effect.[74] The precise role in pregnancy is not known.

VI. TRANSPLACENTAL LIPID TRANSPORT

As mentioned above, lipoprotein lipase is present in the placenta. Recent studies of Bonet et al. indicate that this activity resides both in trophoblast and macrophage cells present in the human placenta.[63] Studies of the rate of metabolism of labeled triglyceride fatty acids in VLDL by human cultured placental trophoblasts or macrophages[63] show approximately fourfold more activity in macrophages per cell protein than in trophoblast (Figure 11). Essentially no lipolytic activity was found in Hep G2 cells, a comparison cultured cell representing typical hepatocyte functions. These lipolytic activities were confirmed as LPL in nature by the addition of antilipoprotein lipase antibodies which blocked the entire effect. When compared to the uptake of FFA, VLDL-TG as a more efficient deliverer of fatty acid to cells than FFA itself, confirming studies in the guinea pig model.[75] This effect could further facilitate the delivery of essential as well as other dietary fatty acids contained in chylomicrons to the placenta. Evidence that these processes may be subject to regulation was obtained when lipolytic activity of macrophages and trophoblasts was studied in the presence of dibutyrylcyclic AMP (Figure 12) and activity was sharply reduced. However insulin had no effect on activity (Figure
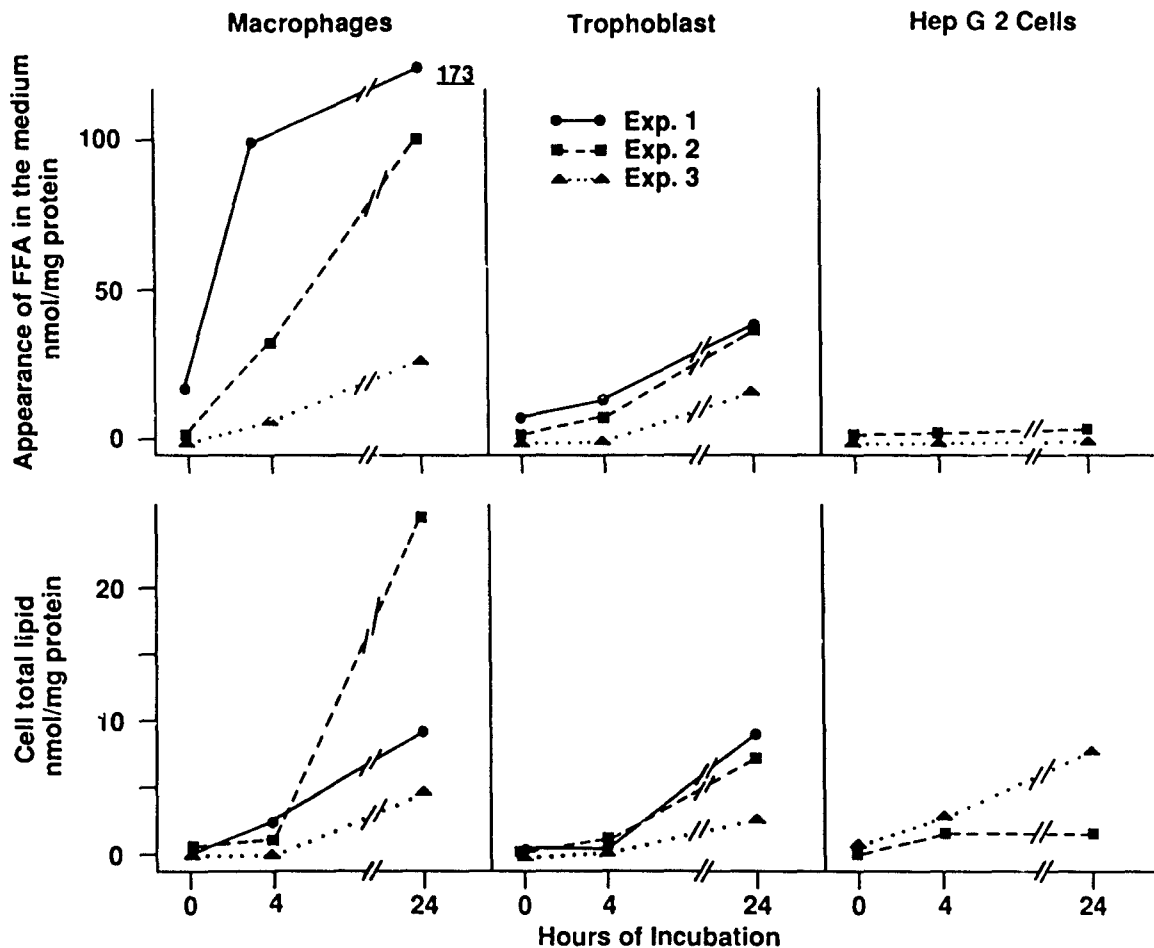
FIGURE 11. Demonstration of the radiolabeled VLDL triglyceride fatty acid hydrolysis *in vitro* by cultured placental macrophages and trophoblasts from human term pregnancy. Appearance of radiolabeled FFA in the medium was demonstrated in the presence of macrophages and trophoblasts in a time-dependent manner. Activity is greater in macrophages than trophoblasts as shown. Little or no activity is shown in Hep G2 cells, an immortal hepatoma cell line. Corresponding uptake of fatty acids labeled by the cells is shown in the bottom panels. Results are from three parallel experiments in separate placentas. (Previously unpublished data of Bonet, B. and Knopp, R. H.) (See Reference 63 for further details.)

12), nor does diabetes apparently alter the activity of placental LPL.[32,76] The importance of this observation is that triglyceride-rich lipoproteins such as VLDL and chylomicrons, if further increased as in Type II diabetes, can further augment fat transfer to the fetus and possibly contribute to infant macrosomia.

The role of triglyceride fatty acid transport across the placenta has not been directly studied in humans, but following an *in situ* placental infusion technique in the late pregnant rat, no direct transfer of prelabeled VLDL-TG could be shown.[77] However, evidence shows that FFA achieve a ready transfer across the placenta in the subhuman primate model as well as several other species including the guinea pig, rabbit, and rat,[2,76–79] and that human-cultured placental trophoblast secretes FFA.[80] In fact, transplacental gradients of FFA have been found along with a positive statistical correlation between maternal and fetal FFA concentrations (see Reference 32 for review). Very recently,
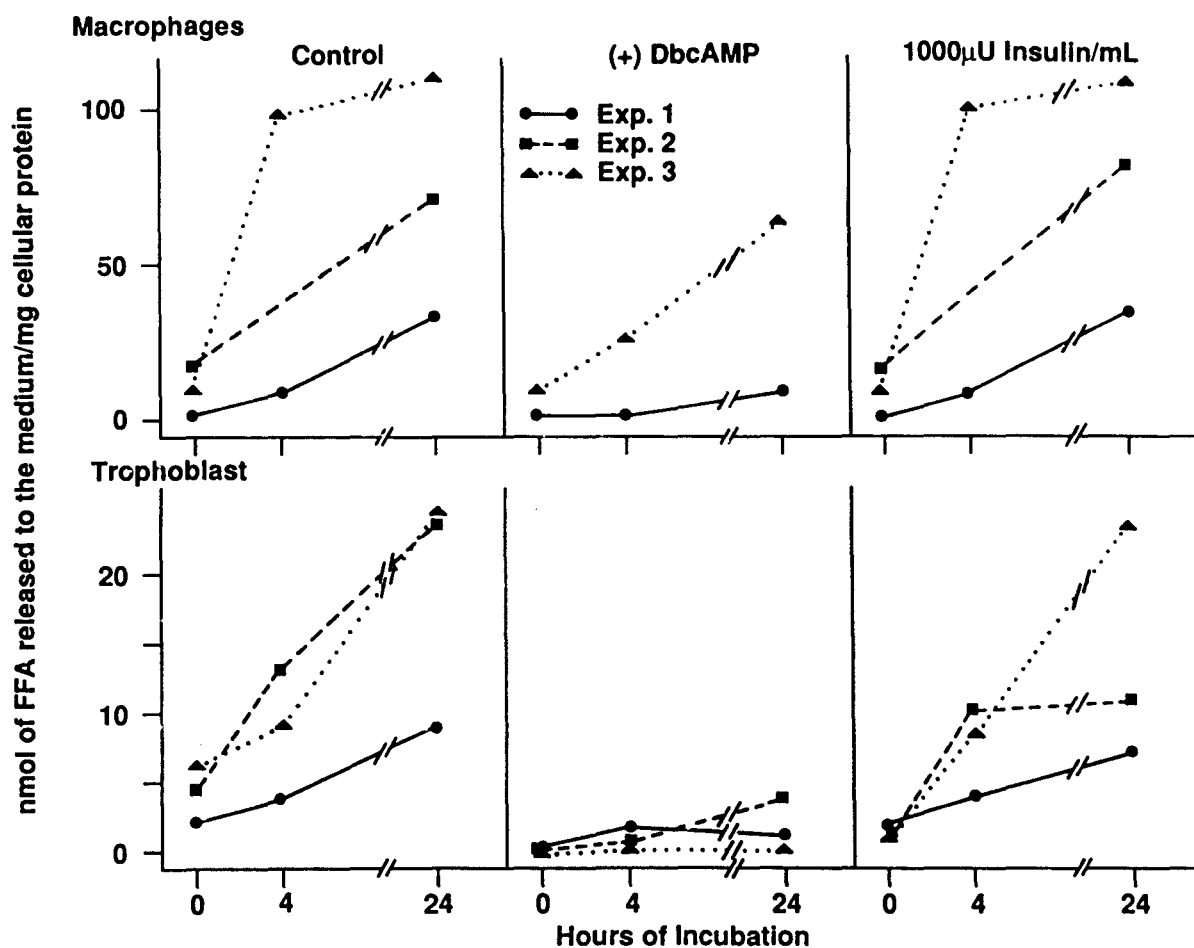
Macrophages

Control (+) DbcAMP 1000µU Insulin/mL

●——● Exp. 1
■--■ Exp. 2
▲···▲ Exp. 3

100

50

0

Trophoblast

20

10

0

nmol of FFA released to the medium/mg cellular protein

0 4 24   0 4 24   0 4 24

Hours of Incubation

FIGURE 12. Effect of insulin (1 milliunit/ml) and dibutyryl cyclic AMP(DbcAMP)(1 mM) on LPL activity in placental cells and tissue culture. Experiments are similar to those presented in Figure 11. Time-dependent increase in hydrolysis of radiolabeled VLDL by cultured macrophages (top panels) and trophoblasts (bottom panels) from term human placentas increase with incubation over time. DbcAMP appears to inhibit this process, whereas insulin has no effect. (Previously unpublished data of Bonet, B. and Knopp, R. H.) (See Reference 63 for further details.)

red cells have been found to play a specific role in the uptake and transport of the essential fatty acid docosahexanoic acid.[81] Other fatty acids follow a similar but less marked trend.[81] No statistically significant gradient has been found for triglyceride except during infusion of a fat emulsion to pregnant women.[82] In addition, in the streptozotocin diabetic 20-d-pregnant rat treated with different amounts of exogenous insulin to attain a variety of glycemic levels, we found a linear and significant correlation between maternal and fetal plasma triglyceride levels (Herrera, E., Martin, A., and Domínguez, M., unpublished results). Thus, the possibility is not excluded that placental FFA that are reesterified to triglyceride[83] might be repackaged into a lipoprotein and secreted from the placenta into the fetal circulation. For this packaging to occur, placental synthesis of either apoprotein B or apoprotein A-I would be necessary. In fact, RNA message for apoprotein B is present in the rat placenta[84] but so far has not been found in the human.[85] Regardless of mechanisms, the important practical point is that maternal plasma FFA[86,87]

and triglyceride concentrations[88,89] are associated with infant birthweight. In the case of triglyceride, the association with birthweight persists even when other maternal predictors are taken into account.[88]

With respect to cholesterol uptake by the placenta, the LDL receptor has been clearly demonstrated by Lasunción et al. to be active in the process of taking up LDL[90] since chemical modification of the apoprotein B of LDL,as well as antibody to the LDL receptor, blocks LDL-mediated progesterone secretion by cultured human trophoblast cells. These maneuvers confirm and extend the earlier studies of Winkel, Cummings, and associates.[91,92] Some evidence exists that the placental LDL receptor is estrogen influenced, since an anti-estrogen downregulates the placental cell LDL receptor activity.[93] In addition, a nonreceptor-mediated mechanism for HDL_2-C uptake by the placenta has been demonstrated by Lasunción and associates.[90] In these investigations it was found that HDL_2 stimulates progesterone secretion by cultured human placental cells but this process was not inhibitable by any of the known modifiers of LDL access to receptors. In addition, maneuvers that specifically inactivate HDL apoprotein also did not inhibit the transfer of cholesterol from the cells. Even apo E was ruled out as a possible mediator of this effect.[90] The effect of HDL_2 to transfer cholesterol to the placenta was localized to a small apo E rich, free-cholesterol-rich fraction of HDL_2 and it was inferred that the amount of free cholesterol in HDL_2 determines the amount of transfer to the placenta along a concentration gradient.

The role of HDL_2 to deliver cholesterol to the trophoblast could in part explain the reduction in HDL-C concentrations in the second half of pregnancy when progesterone manufacture peaks.[31,32] This finding could also explain the positive association between HDL-C concentrations and progesterone levels (Table 3).[32] It is also noteworthy that HDL stimulates placental cyclic AMP and placental lactogen secretion in cultured human trophoblast via apoproteins A-I, A-II, and C-I.[94]

In contrast to the cholesterol donating effect of HDL_2, HDL_3 in parallel studies was found to inhibit the production of progesterone by trophoblast cells and to reduce the intracellular content of free cholesterol.[90] This process of reverse cholesterol transport may be HDL receptor mediated since a candidate protein for the HDL receptor is present in placenta.[95] The possible mechanisms of lipoprotein lipid access to the placenta and fetus are illustrated in Figure 13. The relationship of the placenta to the postulated increased lipoprotein traffic in pregnancy is illustrated in Figure 14. This increase does not appear to be associated with any increase in sterol loss from the mother since biliary lipid excretion is not increased in pregnancy.[96]

The possible significance for the fetus of these lipoprotein interactions with placenta was investigated in a cross-sectional study of lipoprotein lipid concentrations at 36-weeks gestation related to infant birthweight (Figure 15).[97] It was found that apoprotein A-I had a positive association with birthweight as did human placental lactogen concentrations and maternal weight and weight gain. In contrast, apoprotein A-II had an inverse association with
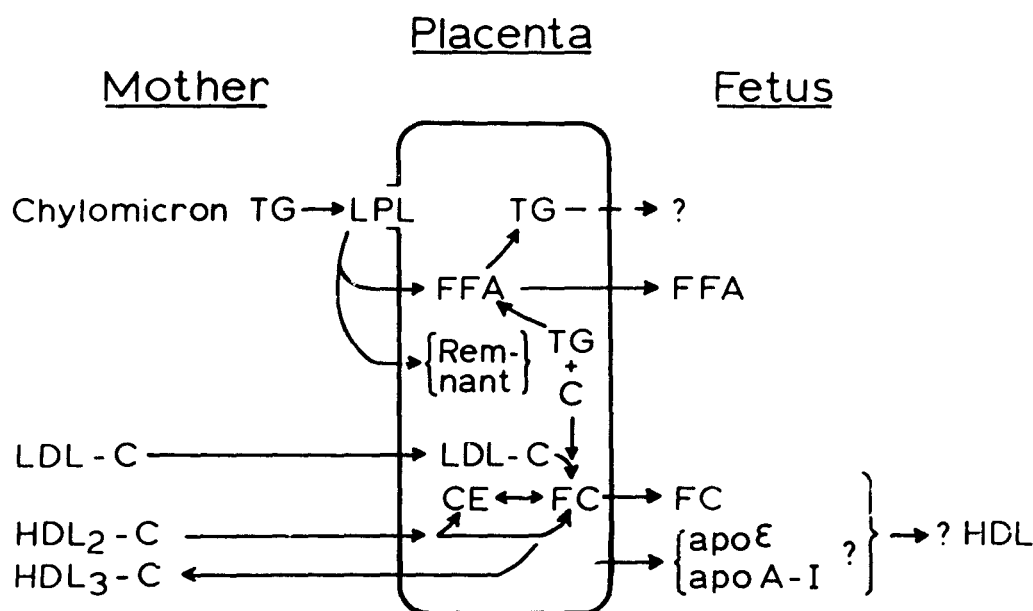
FIGURE 13. Hypothetical model of lipoprotein lipid transport across the placenta. Maternal lipoprotein lipids on the left side of the illustration are depicted as reaching the placenta and then undergoing metabolism with selected transfer to the fetus. Chylomicron triglycerides do not enter the placenta directly but are hydrolyzed by lipoprotein lipase to FFA. The possibility of remnant lipoprotein uptake derived from chylomicron of VLDL metabolism has not been ruled out and is therefore depicted in this illustration. FFA within the placenta are secreted to the fetus or can be reesterified to triglyceride. Whether triglyceride can be secreted directly to the fetus is unknown. LDL-C concentrations interact with the placenta via the LDL receptor whereas HDL_2-C delivers cholesterol to the placenta by a nonreceptor mediated mechanism. Reverse cholesterol transport of cholesterol from the placenta occurs via HDL_3. Cholesterol transport from mother to fetus has been demonstrated, however the mechanism for this is unknown and could involve the secretion of nascent HDL. Alternatively, apo B containing lipoproteins may be secreted by the placenta. See text for further discussion. (From Knopp, R. H., Magee, M. S., Bonet, B., and Gomez-Coronado, D., *Principles of Perinatal-Neonatal Metabolism*, Springer-Verlag, New York, 1991, 177. With permission.)

infant birthweight. Since apoprotein A-I is most abundant in HDL_2 while apoprotein A-II is more predominant in HDL_3 concentrations, these apoprotein associations with birthweight support the idea that HDL_2 delivers cholesterol to the fetus, benefitting growth, and HDL_3 reduces cholesterol to the fetus, inhibiting growth. It is noteworthy, as shown in Figure 15, that similar relationships between apoprotein A-I and A-II were seen with birth length.[97] Direct cause and effect relationships remain to be demonstrated.

VII. EFFECTS OF LACTATION ON LIPOPROTEIN METABOLISM

As indicated above, mammary gland lipoprotein lipase activity rises near term in preparation for lactation[56-58] and prolactin seems to promote this effect.[98] As shown in Figure 16, in untreated pregnant rats (continuous lines in the figure) the rise in mammary gland LPL activity during late gestation and postpartum occurs in the presence of very low LPL activity in adipose
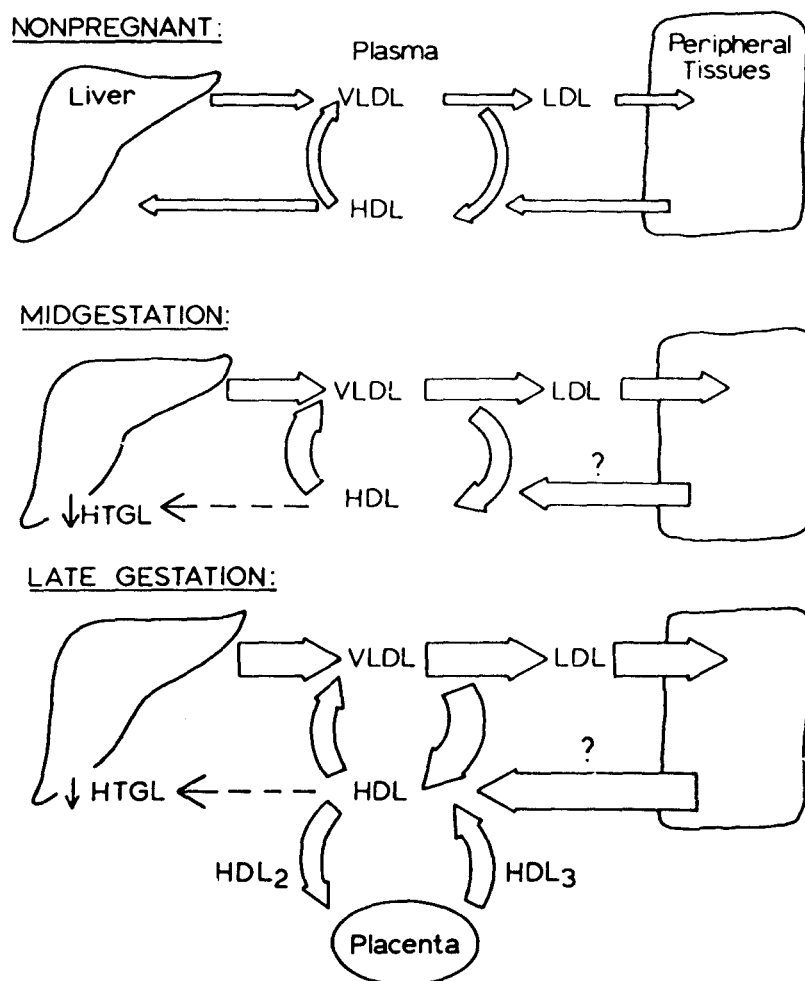
FIGURE 14. Depiction of the changes in lipoprotein lipid transport in nonpregnant midgestational to late-gestational human pregnancy. Endogenous lipoproteins originate from the liver and deliver triglyceride and cholesterol to peripheral tissues via the metabolism of VLDL and LDL. Reverse cholesterol transport is mediated by HDL with transfer of surface constituents from VLDL to LDL and from HDL to VLDL, depending on chylomicron/VLDL concentration and rate of metabolism. In midgestation, all of these pathways are enhanced, presumably with more recycling of HDL constituents to the VLDL/LDL cascade in light of the estrogen-dependent reduction in hepatic lipase activity (HTGL). Lipoprotein transport is depicted as further increased in late gestation; however, the enlargement of the placenta may play a more important role in the diversion of HDL_2-C to the placenta for the formation of progesterone. HDL_3 is shown as being involved in reverse cholesterol transport. Diversion of HDL_2-C to placenta may account for the decline in HDL-C concentrations in late gestation. See text for details and Figure 3. (From Knopp, R. H. et al., *Principles of Perinatal-Neonatal Metabolism*, Cowett, R. M., Ed., Springer-Verlag New York, 1991, 177. With permission.)

tissue and is coincident with the decrease in plasma triglycerides indicating a relationship between these parameters. In fact, as also shown in Figure 16, when rats are treated with progesterone (dotted lines) to block the rise in prolactin[58] and therefore to inhibit its effect on mammary gland LPL induction, the decrease of plasma triglycerides around parturition does not occur. These findings, together with the enhanced uptake by mammary gland of labeled triglycerides after its oral load that is seen in late pregnant rats,[51]

	Apoproteins	Lipoprotein Lipids	Fuels, Hormones	Mother Characteristics	Clinical Chemistries

A. BIRTH
WEIGHT
PREDICTORS:

				Weight		
(+)	A-I		HPL	Weight Gain	Billirubin	Birth Weight
(-)	A-II	VLDL-C			SGOT, Creat	
(r²) IC:	--	0.05	0.11	0.12	0.10	
RS:	0.08	0.09	--	0.15	--	

B. BIRTH
LENGTH
PREDICTORS:

(+)	A-I		HPL	Weight		Birth Length
(-)	A-II					
(r²) IC:	--	0.02	0.05	0.06	0.03	
RS:	0.15	0.15	--	0.11	--	

C. HEAD
CIRCUM-
FERENCE
PREDICTORS:

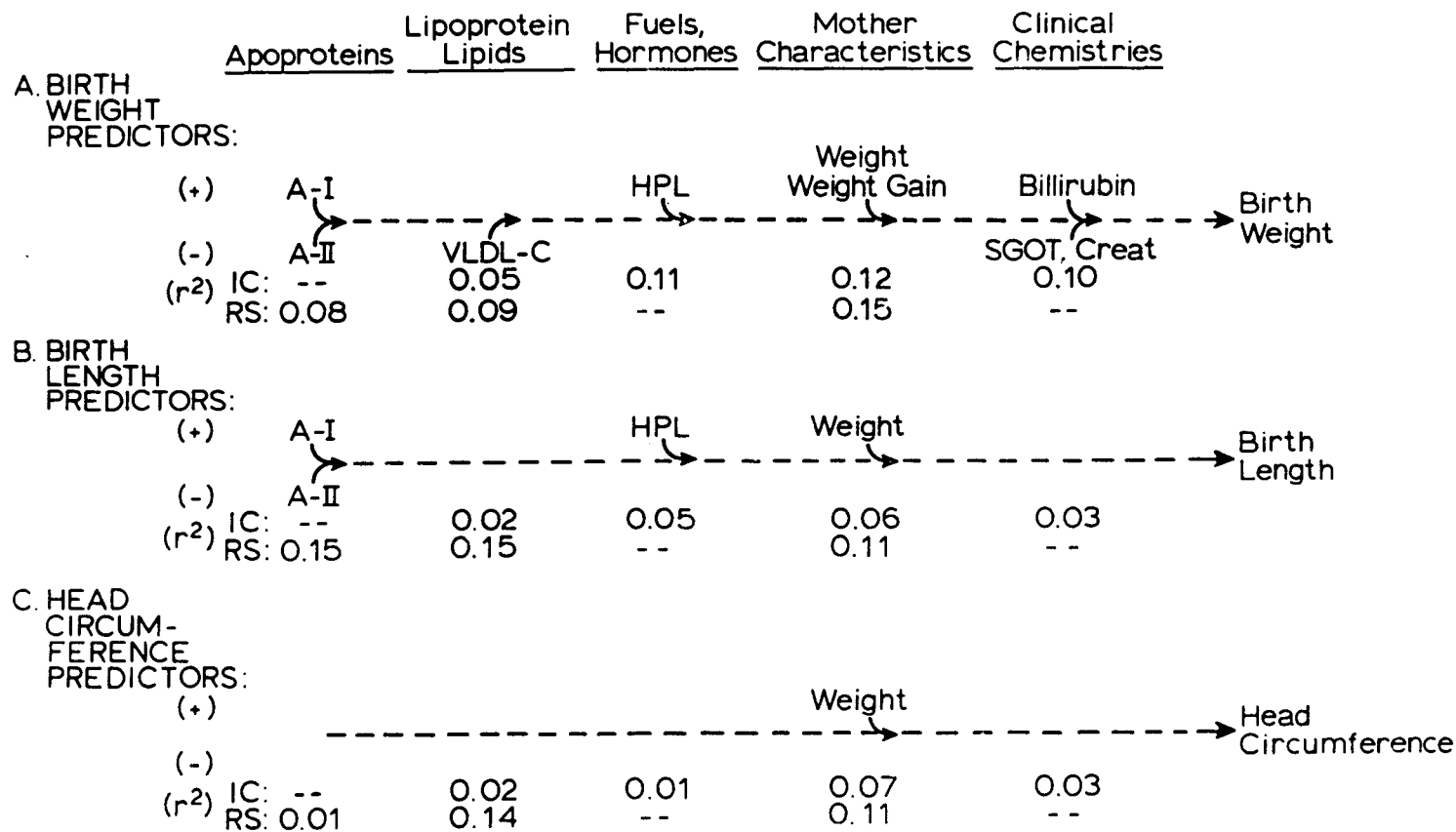|				Weight		
(+)						Head Circumference
(-)						
(r²) IC:	--	0.02	0.01	0.07	0.03	
RS:	0.01	0.14	--	0.11	--	

FIGURE 15. Prospectively determined associations between maternal apoprotein; lipoprotein lipids; fuel and hormone levels; maternal characteristics; and clinical chemistries with (A) fetal birthweight,[16] (B) birth length, and (C) head circumference. The most important point is that apoprotein A-I is a positive predictor of birthweight and apoprotein A-II is a negative predictor both of birthweight and birth length, suggesting a role for HDL_2 and HDL_3, respectively, in cholesterol transport to and from the placenta. See text for discussion of possible effects on placental progesterone secretion. Expected associations between placental lactogen, maternal weight, and weight gain are also seen on birthweight and birth length. Surprisingly, bilirubin is a positive predictor of birthweight while SGOT and creatinine concentrations are negative predictors. Only maternal weight is a predictor of head circumference. Numerical values shown are the R^2 values for an initial cohort (IC) and a random sample (RS) of subjects studied in this investigation. See text and Reference 97 for further details. (From Knopp et al., *Diabetes*, 34 (Suppl. 2), 71, 1985. Copyright© 1985 by the American Diabetes Association. Reprinted with permission.)

CONTROLS ●────● **PROGESTERONE** (7mg/rat/day)
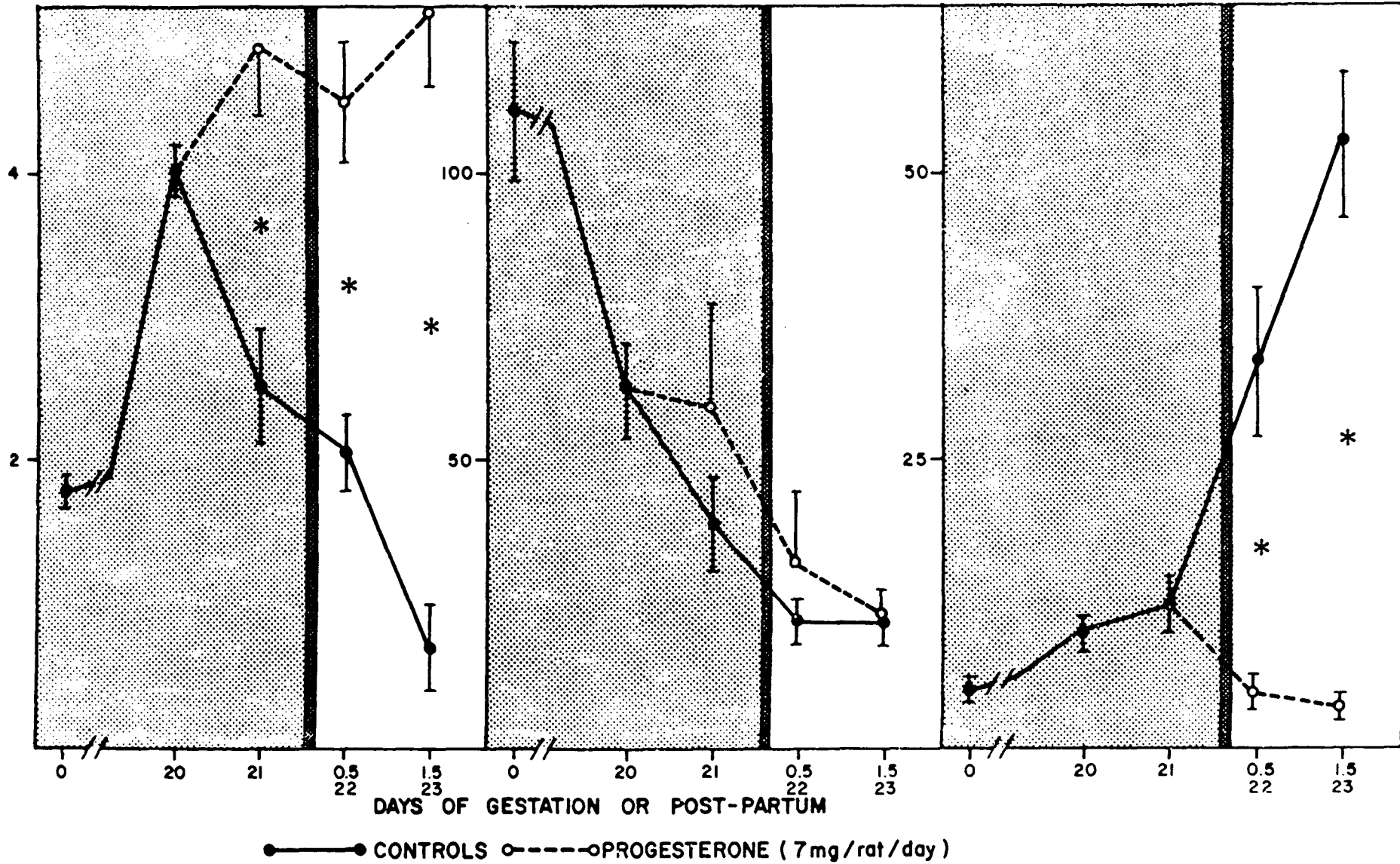
FIGURE 16. Effect of progesterone administration near parturition in rat pregnancy to reverse the reduction in plasma triglyceride and the rise in mammary gland LPL activity. It is postulated that the progesterone effect is mediated by the progesterone inhibition of prolactin secretion. Controls, ●────●; progesterone (7 mg/rat/day),○────○. See Reference 58 and text for details.

indicate that the increase in mammary gland lipoprotein lipase activity plays an important role in the reduction of circulating triglycerides, facilitating their entry into the gland. In spite of the reciprocal changes of adipose tissue and mammary gland LPL activities found during late pregnancy and lactation, their responses to nutritional stresses are similar. Both of them decrease with fasting and increase with insulin treatment (Herrera, E., Ramos, P., Olea, J., and López-Luna, P., unpublished results) and in fact it has been recently proposed that mammary gland LPL originates in the mammary adipocytes.[99] In humans, breast milk also contains LPL activity at high concentrations[98] which is decreased by fasting and increased under hyperinsulinemic and hyperglycemic conditions.[98] The function of milk LPL is unknown since the enzyme is probably not active in milk due to the absence of the serum factor, apolipoprotein C-II, necessary for its activity. However, since circulating long-chain fatty acids appear in breast milk[100] and dietary lipids have been shown in lactating women to be transported to the mammary gland primarily by chylomicron and VLDL triglycerides,[100] it is proposed that LPL in milk is a reflection of the enzyme present in mammary gland where LPL plays a major role in the hydrolysis and uptake of circulating triglycerides from triglyceride-rich lipoproteins. Consequently, as shown in Table 4, plasma lipoproteins postpartum show higher HDL lipids and apoprotein A-I concentrations in lactating women compared to nonlactating women. Comparing absolute concentrations, it appears that plasma VLDL triglyceride concentrations may be lower during lactation compared to nonlactators, however, this effect was not statistically different when adjusting for antepartum differences[101] (Table 4). What may happen is that the increased triglyceride transport to the breast increases transfer of surface remnants to HDL explaining the increase in HDL mass.

VIII. DISORDERS OF LIPOPROTEIN METABOLISM IN PREGNANCY

Severely exaggerated hypertriglyceridemia in pregnancy can develop in late gestation. This condition can lead to pancreatitis if the plasma triglyceride concentrations exceed approximately 2000 mg/dl. Treatment of this condition consists of marked restriction of fat intake. Success can also be achieved through the administration of fish oils 1 to 8 g daily.[102] In one pregnant woman with a history of hyperlipidemia and pancreatitis in a previous pregnancy, fish oil relieved abdominal pain and hypertriglyceridemia and the patient delivered a normal viable infant.[102] We have also found some women who develop hypertriglyceridemia in pregnancy but become normal postpartum and have suggested that these patients may be "prelipemic," analogous to gestational diabetes.[103] Some of these subjects actually have a decline in HDL-C during pregnancy and have a low HDL-C as a permanent postpartum marker.[103] Women with elevated LDL-C when not pregnant and those with familial hypercholesterolemia develop further elevations in pregnancy.[103] These

TABLE 4
Effects of Lactation on Lipoproteins

Lipoproteins	Postpartum concentrations (mg/dl)			Antepartum—postpartum difference (mg/dl)		
	Lac	Nonlac	*p*	Lac	Nonlac	*p*
Total	56	16		56	16	
TG	92	112	<0.02	129	116	NS
Chol	207	188	<0.01	39	50	NS
VLDL	54	78	<0.01	63	57	NS
TG						
Chol	14	17	NS	14	12	NS
LDL	26	24	NS	44	35	NS
TG						
Chol	129	121	NS	25	21	NS
PL	70	70	NS	15	15	NS
Apo-B	76	66	NS	29	24	NS
HDL	12	10	NS	20	22	NS
TG						
Chol	65	51	<0.001	−1	17	<0.0001
PL	141	123	<0.005	1	23	<0.01
Apo A-I	142	126	<0.02	31	46	<0.01
Apo A-II	34	31	<0.01	−3	4	<0.001

Note: Abbreviations: TG = triglyceride; Chol = cholesterol; PL = phospholipid; Lac = lactating; NS = not significant.

From Knopp, R. H., Walden, C. E , and Albers, J. J., *J. Clin. Endocrinol. Metab.*, 60, 542, 1985. With permission of The Endocrine Society©.

elevations are partially ameliorated with cholesterol lowering diet.[104,105] Whether such treatment affects fetal growth and development or benefits the mother is unknown. None of the primary dyslipidemias are associated with reproductive abnormality as far as we know (example Reference 106) with the exception of severe hypertriglyceridemia and pancreatitis as discussed above, which can endanger the life of mother as well as fetus.

Diabetes in pregnancy of the NIDDM type is associated with hypertriglyceridemia[88,107] and a low HDL-C[107] as is preeclampsia.[42] Type I diabetics have little change in lipoproteins except for a reduction in HDL_3 which could diminish reverse cholesterol transport, augment cholesterol transport to the fetus and promote infant macrosomia.[108] As noted above, experimental diabetes does not appear to alter placental LPL activity.[32,76] However, diabetes may enhance oxidative stress on lipoproteins which, in susceptible individuals, could activate uptake of oxidized or modified lipoproteins by placental macrophages via the scavenger receptor.[109] Very recently, Bonet has found evidence for the scavenger receptor in immunochemically characterized cultured human placental trophoblast cells as well,[109] in keeping with the results of

Rebourcet et al., who have found scavenger receptor activity in placental microvilli membranes[110] and cultured placental cells.[111] This group has also found evidence for chemically modified LDL in placental blood.[112] These findings may have great pathophysiological significance in diabetic pregnancy.

IX. SUMMARY AND CONCLUSIONS

Changes in lipoprotein metabolism in pregnancy occur in a defined relationship to changes in the metabolism of other fuels in pregnancy. Specifically, lipoprotein lipid concentrations increase in all fractions throughout pregnancy except for a biphasic rise and fall in HDL-C. These changes appear to be directly or indirectly associated with the sex steroid increases throughout gestation and the insulin resistance and glucose intolerance of late gestation. Mechanisms exist for the regulated transfer of maternal lipoprotein lipids, both triglyceride and cholesterol, to the fetal circulation as well as the interception of abnormal lipoprotein. Evidence exists for associations between the maternal plasma FFA, triglyceride, and HDL apoprotein concentrations with birthweight and for direct effects of LDL and HDL_2 and HDL_3 on placental progesterone secretion. These results indicate that maternal lipoprotein lipids have an effect on fetal growth and development and hormone secretion by the feto-placental unit. It follows that adverse effects of maternal diabetes on lipoproteins could in turn adversely affect fetal growth and development in a number of ways. Current research is directed at examining these possible mechanisms and consequences.

ACKNOWLEDGMENTS

REFERENCES

1. **Knopp, R. H. and Magee, M. S.,** Physiological changes in pregnancy, in *Textbook of Physiology,* Vol. 2, 21st ed., Patten, H. D., Fuchs, A., Hille, B., Scher, A., and Steiner, R., Eds., W.B. Saunders, Philadelphia, 1989, 1380.
2. **Knopp, R. H., Magee, M. S., Bonet, B., and Gomez-Coronado, D.,** Lipid metabolism in pregnancy, in *Principles of Perinatal-Neonatal Metabolism,* Cowett, R. M., Ed., Springer-Verlag, New York, 1991, 177.
3. **Knopp, R. H.,** Sex hormone control of triglyceride metabolism, in *Arteriosclerosis Reviews,* Vol. 22, Goho, A. M., Jr. and Paoletti, R. O., Eds., Raven Press, New York, 1991, 33.
4. **Knopp, R. H.,** Estrogen replacement therapy for reduction of cardiovascular risk in women, *Curr. Opin. Lipidol.,* 2, 240, 1991.

5. **Knopp, R. H.,** The effects of oral contraceptives and postmenopausal estrogens on lipoprotein physiology and atherosclerosis, in *Oral Contraception Into the 1990's*, Parthenon Publishing, Camforth, U.K., 1989, 31.

6. **Iverius, P. H. and Brunzell, J. D.,** Relationship between lipoprotein lipase activity and plasma sex steroid level in obese women, *J. Clin. Invest.*, 82, 1106, 1988.

7. **Applebaum-Bowden, D., McClean, P., Steinmetz, A., Fontana, D., Matthys, C., Warnick, G. R., Cheung, M., Albers, J. J., and Hazzard, W. R.,** Lipoprotein, apolipoprotein, and lipolytic enzyme changes following estrogen administration in postmenopausal women, *J. Lipid Res.*, 30, 1895, 1989.

8. **Beisiegel, U., Wilfried, W., Ihrke, G., Herz, J., and Stanley, K. K.,** The LDL-receptor-related protein, LRP, is an apolipoprotein E-binding protein, *Nature*, 341, 162, 1989.

9. **Kowal, R. C., Herz, J., Goldstein, J. L., Esser, V., and Brown, M. S.,** Low density lipoprotein receptor-related protein mediates uptake of cholesterol esters derived from apoprotein E-enriched lipoproteins, *Proc. Natl. Acad. Sci. U.S.A.*, 86, 5810, 1989.

10. **Berr, F., Eckel, R. H., and Kern, F. Jr.,** Contraceptive steroids increase hepatic uptake of chylomicron remnants in healthy young women, *J. Lipid Res.*, 27, 645, 1986.

11. **Schaefer, E. J., Foster, D. M., Zech, L. A., Lindgren, F. T., Brewer, H. B., Jr., and Levy, R. I.,** The effects of estrogen administration on plasma lipoprotein metabolism in premenopausal females, *J. Clin. Endocrinol. Metab.*, 57, 262, 1983.

12. **Kovanen, P. T., Brown, M. S., and Goldsten, J. L.,** Increased binding of low density lipoproteins to liver membranes from rats treated with 17 alpha-ethinyl estradiol, *J. Biol. Chem.*, 254, 11367, 1979.

13. **Ma, P. T. S., Yamamoto, T., Goldstein, J. L., and Brown, M. S.,** Increased mRNA for low density lipoprotein receptor in livers of rabbits treated with 17 alpha-ethinyl estradiol, *Proc. Natl. Acad. Sci. U.S.A.*, 83, 792, 1986.

14. **Chait, A., Brunzell, J. D., Albers, J. J., and Hazzard, W. R.,** Type III hyperlipoproteinemia ("remnant removal disease"): insight into the pathogenetic mechanism, *Lancet*, 1, 1176, 1977.

15. **Hazzard, W. R.,** Primary type I hyperlipoproteinemia, in *Hyperlipidemia—Diagnosis and Therapy*, Rifkin, B. M. and Levy, R. I., Eds., Grune & Stratton, Orlando, 1977, 137.

16. **Arbeeny, C. M. and Eder, H. A.,** Effects of 17 alpha-ethinyl estradiol on the serum lipoproteins of cholesterol fed diabetic rats, *J. Biol. Chem.*, 255, 10547, 1980.

17. **Graham, D. L. and Oram, J. F.,** Characterization of a high density lipoprotein-binding protein in cell membranes by ligand blotting, *J. Biol. Chem.*, 262, 7439, 1987.

18. **Hazzard, W. R., Haffner, S. M., Kushwaha, R. S., Applebaum-Bowden, D., and Foster, D. M.,** Preliminary report kinetic studies on the modulation of high-density lipoprotein, apolipoprotein, and subfraction metabolism by sex steroids in a postmenopausal woman, *Metabolism*, 33, 779, 1984.

19. **Tikkanen, M. J., Kuusi, T., Nikkilä, E. E. A., and Stenman, U. H.,** Variation of postheparin plasma hepatic lipase by menstrual cycle, *Metabolism*, 35, 99, 1986.

20. **Bamberger, M., Glick, J. M., and Rothblat, G. H.,** Hepatic lipase stimulates the uptake of high density lipoprotein cholesterol by hepatoma cells, *J. Lipid Res.*, 24, 869, 1983.

21. **McPherson, R., Mann, C. J., Tall, A. R., Hogue, M., Martin, L., Milne, R. W., and Marcel, Y. L.,** Plasma concentrations of cholesteryl ester transfer protein in hyperlipoproteinemia, *Arterioscl. Thromb.*, 11, 797, 1991.

22. **Appebaum-Bowden, D., McLean, P., Steinmetaz, A., Fontana, D., Matthys, C., Warnick, G. R., Cheung, M., Albers, J. J., and Hazzard, W. B.,** Lipoprotein, apolipoprotein, and lipolytic enzyme changes following estrogen administration in postmenopausal women, *J. Lipid Res.*, 30, 1895, 1989.

23. **Ottoson, U.-B.,** Oral progesterone and estrogen/progestogen therapy, *Acta Obstet. Gynecol.*, Suppl. 127, 5, 1984.

24. **Knopp, R. H., Walden, C. E., Wahl, P. W., Warnick, G. R., Albers, J. J., Ogilvie, J. T., Hazzard, W. R., and Hoover, J.J.,** Oral contraceptive and postmenopausal estrogen effects on lipoprotein triglyceride and cholesterol in an adult female population: relationships to estrogen and progestin potency, *J. Clin. Endocrinol. Metab.,* 53, 1123, 1981.

25. **Kohkha, R., Huff, M. W., and Wolfe, B. M.,** Divergent effects of d-norgestrel on the metabolism of rat very low density and low density apolipoprotein B, *J. Lipid Res.,* 27, 699, 1986.

26. **Wolfe, B. M. and Grace, D. M.,** Norethindrone acetate inhibition of splanchnic triglyceride secretion in conscious glucose-fed swine, *J. Lipid Res.,* 20, 175, 1979.

27. **Kenagy, R., Weinstein, I., and Heimberg, M.,** The effects of 17-beta-estradiol and progesterone on the metabolism of free fatty acid by perfused livers from normal female and ovariectomized rats, *Endocrinology,* 108, 1613, 1981.

28. **Walden, C. E., Knopp, R. H., Wahl, P. W., Beach, K. W., and Strandness, D. E. Jr.,** Sex differences in the effect of diabetes mellitus on lipoprotein triglyceride and cholesterol concentrations, *N. Engl. J. Med.,* 311, 953, 1984.

29. **Magee, M. S., Knopp, R. H., Pierce, C., Kranz, J., Fish, B., and Walden, C. E. (Sponsor: C. J. Goodner),** Effects of low-dose multiphasic oral contraceptives over one year on total and LDL-C in comparison to preceding and succeeding normal menstrual cycles, in *Program 71st Annu. Meet. Endocrine Soc.,* Seattle, WA, Abstract #1637, June 21–24, 1989, 432.

30. **Knopp, R. H.,** Cardiovascular effects of endogenous and exogenous sex hormones over a woman's lifetime, in *Prevention and Management of Cardiovascular Risk in Women,* Knopp, R. H. and Mishell, D. R., Jr., Eds., *Am. J. Obstet. Gynecol.,* 158(#6, part 2), (supplement), 1988, 1630.

31. **Knopp, R. H., Montes, A., Childs, M., Li, J. R., and Mabuchi, H.,** Metabolic adjustments in normal and diabetic pregnancy, *Clin. Obstet. Gynecol.,* 24, 21, 1981.

32. **Knopp, R. H., Warth, M. R., Charles, D., Childes, M., Li, J. R., Mabuchi, H., and Van Allen, M.,** Lipoprotein metabolism in pregnancy, fat transport to the fetus, and the effects of diabetes, *Biol. Neonate (Paris),* 50, 297, 1986.

33. **Knopp, R. H., Bergelin, R. O., Wahl, P. W., and Walden, C. E.,** Effects of pregnancy, postpartum lactation and oral contracpetive use on the lipoprotein cholesterol/triglyceride ration, *Metabolism,* 34, 893, 1985.

34. **Fähraeus, L., Larsson-Cohn, U., and Wallentin, L.,** Plasma lipoproteins including high density lipoprotein subfractions during normal pregnancy, *Obstet. Gynecol.,* 66, 468, 1985.

35. **Desoye, G., Schweditsch, M., Pfieffer, K. P., Zechner, R., and Kostner, G. H.,** Correlation of hormones with lipid and lipoprotein levels during normal pregnancy and postpartum, *J. Clin. Endocrinol. Metab.,* 64, 704, 1987.

36. **Herrera, E., Lasunción, M. A., Gomez-Coronado, D., Aranda, P., López-Lunda, P., and Maier, I.,** Role of lipoprotein lipase activity on lipoprotein metabolism and the fate of circulating triglycerides in pregnancy, *Am. J. Obstet. Gynecol.,* 158, 1575, 1988.

37. **Potter, J. M. and Nestel, P. J.,** The hyperlipidemia of pregnancy in normal and complicated pregnancies, *Am. J. Obstet. Gynecol.,* 133, 165, 1979.

38. **Knopp, R. H., Montes, A., and Warth, M. R.,** Carbohydrate and lipid metabolism in normal pregnancy, in *Laboratory Indices of Nutritional Status in Pregnancy,* Food and Nutrition Board, Eds., National Academy of Sciences, Washington, D.C., 1978, 35.

39. **Montes, A., Walden, C. E., Knopp, R. H., Cheung, M., Chapman, M. B., and Albers, J. J.,** Physiologic and supraphysiologic increases in lipoprotein lipids and apoproteins in late pregnancy and postpartum: possible markers for the diagnosis of "prelipemia," *Arteriosclerosis,* 4, 407, 1984.

40. **Pocoví, M., Ordovás, J. M., and Grande-Covián, F.,** Plasma lipids and apolipoproteins A and B in human pregnancy, *Revista Española de Fisiologia,* 40, 183, 1984.

41. Stetiz, H.-O., Brockerhoff, P., Holzer, A., Schicketanz, K.-H., Stinner, B., and Rathgen, G. H., Verteilungsmuster von Apolipoprotein A und B in den Lipoprotein-fraktionen des Serums bei Schwangeren und Post Partum, *Z Geburtsh u Perinat*, 191, 243, 1987.

42. Rosing, U., Samsioe, G., Ölund, A., Johansson, B., and Kallner, A., Serum levels of apolipoprotein A-I, A-II and HDL-Cholesterol in second half of normal pregnancy and in pregnancy complicated by pre-eclampsia, *Horm. Metabol. Res.*, 21, 276, 1989.

43. Zechner, R., Desoye, G., Schweditsch, M. O., Pfeiffer, K. P., and Kostner, G. M., Fluctuations of plasma lipoprotein-(a) concentrations during pregnancy and post partum, *Metabolism*, 35, 333, 1986.

44. Knopp, R. H., Bergelin, R. O., Wahl, P. W., Walden, C. E., Chapman, M., and Irvin, S., Population-based lipoprotein lipid reference values for women classified by sex hormone usage, *Am. J. Obstet. Gynecol.*, 143, 626, 1982.

45. Wahl, P. W., Walden, C. E., Albers, J. J., Hoover, J. J., Warnick, G. R., Bergelin, R. O., Ogilvie, J. T., Hazzard, W. R., and Knopp, R. H., Distribution of lipoprotein triglyceride and cholesterol in an adult population by age, sex, and hormone use: the Pacific Northwest Bell Company Health Survey, *Atherosclerosis*, 39, 111, 1981.

46. Montes, A., Humphrey, J., and Knopp, R. H., Lipid metabolism in pregnancy. VI. Lipoprotein composition and hepatic lipids in the fed pregnant rat, *Endocrinology*, 103, 1031, 1978.

47. Argiles, J. and Herrera, E., Lipids and lipoproteins in maternal and fetal plasma in the rat, *Biol. Neonate*, 39, 37, 1981.

48. McMahan, M. R., Clarkson, T. B., Sackett, G. P., and Rudel, L. L., Changes in Plasma Lipids and Lipoproteins in *Macaca nemestrina* during pregnancy and the post-partum period, *Proc. Soc. Exp. Biol. Med.*, 164, 199, 1980.

49. Koritnik, D. R., Wood, L. L., Shandilya, L. N., and Rudel, L. L., Lipids, lipoproteins, and endocrine profiles during pregnancy in the African Green monkey *(Cercopithecus aethiops)*, *Metabolism*, 33, 840, 1984.

50. Martin, D. E., Wolf, R. C., and Meyer, R. K., Plasma lipid levels during pregnancy in the Rhesus Monkey *(Macaca mulatta)*, *Proc. Soc. Exp. Biol. Med.*, 138, 638, 1971.

51. Argiles, J. and Herrera, E., Appearance of circulating and tissue ^{14}C lipids after oral ^{14}C tripalmitate administration in the late pregnant rat, *Metabolism*, 38, 104, 1989.

52. Humphrey, J. L., Childs, M. T., Montes, A., and Knopp, R. H., Lipid metabolism in pregnancy. VII. Kinetics of chylomicron triglyceride removal in fed pregnant rat, *Am. J. Physiol.*, 239 (Endocrinol Metab 2), E81, 1980.

53. Wasfi, I., Weinstein, I., and Heimberg, M., Increased formation of triglyceride from oleate in perfused livers from pregnant rats, *Endocrinology*, 107, 584, 1980.

54. Childs, M. T., Tollefson, J., Knopp, R. H., and Applebaum-Bowden, D., Lipid Metabolism in Pregnancy. VIII. Effects of dietary fat vs. carbohydrate on lipoprotein and hepatic lipids and tissue triglyceride lipases, *Metabolism*, 30(1), 27, 1981.

55. Warth, M. R. and Knopp, R. H., Lipid metabolism in pregnancy. V. Interactions of diabetes, body weight, age and high carbohydrate diet, *Diabetes*, 26, 1056, 1977.

56. Otway, S. and Robinson, D. S., The significance of changes in tissue clearing-factor lipase activity in relation to the lipaemia of pregnancy, *Biochem. J.*, 106, 677, 1968.

57. Hamosh, M., Clary, T. R., Chernick, S. S., and Scow, R. O., Lipoprotein lipase activity of adipose and mammary tissue and plasma triglyceride in pregnant and lactating rats, *Biochim. Biophys. Acta*, 210, 473, 1970.

58. Ramirez, I., Llobera, M., and Herrera, E., Circulating triacylglyceriols, lipoproteins, and tissue lipoprotein lipase activities in rat mothers and offspring during the perinatal period: effect of postmaturity, *Metabolism*, 32, 333, 1983.

59. Gray, J. M. and Greenwood, M. R. C., Uterine and adipose lipoprotein lipase activity in hormone treated and pregnant rats, *Am. J. Physiol.*, 245, E132, 1983.

60. Mallov, S. and Alousi, A. A., Lipoprotein lipase activity of rat and human placenta, *Proc. Soc. Exp. Biol. Med.*, 119, 301, 1965.

61. **Knopp, R. H., Boroush, M. A., and O'Sullivan, J. B.**, Lipid metabolism in pregnancy. II. Postheparin lipolytic activity and hypertriglyceridemia in the pregnant rat, *Metabolism,* 24, 481, 1975.

62. **López-Lunda, P., Maier, I., and Herrera, E.**, Carcass and rissue fat content in the pregnant rat, *Biol. Neonat.,* 60, 29, 1991.

63. **Bonet, B., Knopp, R. H., Brunzell, J., and Gown, A.**, Metabolism of very low density lipoprotein triglyceride by human placental cells: the role of lipoprotein lipase, *Metabolism,* in press.

64. **Warth, M. R., Arky, R. A., and Knopp, R. H.**, Lipid metabolism in pregnancy. III. Altered lipid composition in intermediate, very low, low and high density lipoprotein fractions, *J. Clin. Endocrinol. Metab.,* 41, 649, 1975.

65. **Shiomi, M., Takashi, I., and Watanabe, Y.**, Increase in hepatic low-density lipoprotein receptor activity during pregnancy in Watanabe heritable hyperlipidemic rabbits: an animal model for familial hypercholesterolemia, *Biochim. Biophys. Acta,* 917, 92, 1987.

66. **Belknap, W. M. and Dietschy, J. M.**, Sterol synthesis and low density lipoprotein clearance *in vivo* in pregnant rat, placenta, and fetus: sources for tissue cholesterol during fetal development, *J. Clin. Invest.,* 82, 2077, 1988.

67. **Feingold, K. R., Wiley, T., Moser, A. H., Lear, S. R., and Wiley, M. H.**, *De novo* cholestrogenesis in pregnancy, *J. Lab. Clin. Med.,* 101, 256, 1983.

68. **Innis, S. M.**, The activity of 3-hydroxy-3-methylglutaryl-CoA reductase and acyl-CoA: cholsterol acyltransferase in hepatic microsomes from male, female and pregnant rats. The effect of cholestyramine treatment and the relationship of enzyme activity to microsomal lipid composition, *Biochim. Biophys. Acta,* 875, 355, 1986.

69. **Mabuchi, H., Sakai, Y., Watanabe, A., Haba, T., Koizumi, J., and Takeda, R.**, Normalization of low-density lipoprotein levels and disappearance of xanthomas during pregnancy in a woman with heterozygous familial hypercholesterolemia, *Metabolism,* 34, 309, 1985.

70. **Kinnunen, P. K. J., Unnerus, H.-A., Ranta, T., Ehnholm, C., Nikkilä, E. A., and Seppälä, M.**, Activities of post-heparin plasma lipoprotein lipase and hepatic lipase during pregnancy and lactation, *Eur. J. Clin. Invest.,* 10, 469, 1980.

71. **Sakuma, N., Oshima, T., and Knopp, R. H.**, Sex hormone and lipid metabolism: effects of pregnancy on lipoprotein lipids in third trimester Japanese women and HDL apoprotein and cholesterol kinetics in the experimental rat, *J. Jap. Atheroscl. Soc.,* 10, 617, 1982.

72. **Herrera, E., Ramos, P., and Martin, A.**, Control by insulin of adipose tissue lipoprotein lipase activity during late pregnancy in the rat, in *Frontiers in Diabetes Research. Lessons from Animal Diabetes III,* Shafrir, E., Eds., Smith-Gordon, London, 1990, 551.

73. **Herrera, E. and Ramos, P.**, Continuous hyperinsulinema reverses insulin resistance in rat during late gestation, *Diabetologia,* (Abstr.), in press.

74. **Taskinen, M.-R., Kuusi, T., Nikkilä, E. A., and Yki-Jäarvinen, H.**, Insulin therapy induces antiatherogenic changes of serum lipoproteins in moninsulin-dependent diabetes, *Arteriosclerosis,* 8, 168, 1988.

75. **Thomas, C. R., Lowy, C., St. Hillaire, R. J., and Brunzell, J. D.**, Studies on the placental hydrolysis and transfer of lipids to the fetal guinea pig, in *Fetal Nutrition, Metabolism, and Immunology: The Role of the Placenta,* Miller, R. K. and Thiede, H. A., Eds., Plenum Medical, New York, 1984, 135.

76. **Shafrir, E. and Barash, V.**, Placental function in maternal-fetal fat transport in diabetes, *Biol. Neonate,* 51, 102, 1987.

77. **Herrera, E., Lasunción, M. A., and Asunción, M.**, Placental transport of free fatty acids, glycerol and ketone bodies, in *Neonatal and Fetal Medicine: Physiology and Pathophysiology,* Polin, R. and Fox, W., Eds., Grune and Stratton, New York, in press.

78. **Portman, O. W., Behrman, R. E., and Soltys, P.**, Transfer of free fatty acids across the primate placenta, *Am. J. Physiol.,* 216, 143, 1969.

79. **Hershfield, M. S. and Nemeth, A. M.,** Placental transport of free palmitic and linoleic acids in the guinea pig, *J. Lipid Res.,* 9, 460, 1968.

80. **Coleman, R. A. and Haynes, E. B.,** Synthesis and release of fatty acids by human trophoblast cells in culture, *J. Lipid Res.,* 28, 1335, 1987.

81. **Ruyle, M., Connor, W. E., Anderson, G. J., and Lowensohn, R. L.,** Placental transfer of essential fatty acids in humans: venous-arterial differences for docosahexaenoic acid in fetal umbilical erythrocytes, *Proc. Natl. Acad. Sci. U.S.A.,* 87, 7902, 1990.

82. **Elphick, M. C., Filshie, G. M., and Hull, D.,** The passage of fat emulsion across the human placenta, *Br. J. Obstet. Gynecol.,* 85, 610, 1978.

83. **Coleman, R. A.,** The role of the placenta in lipid metabolism and transport, *Seminars in Perinatology.* 13, 180, 1989.

84. **Demmer, L. A., Lavin, M. S., Elovson, J., Reuben, M. A., Lusis, A. J., and Gordon, J. I.,** Tissue-specific expression and developmental regulation of the rat apolipoprotein B. gene, *Proc. Natl. Acad. Sci. U.S.A.,* 83, 8102, 1986.

85. **Deeb, S. S., Motulsky, A., and Albers, J. J.,** A partial cDNA clone for human apolipoprotein B, *Proc. Natl. Acad. Sci. U.S.A.,* 82, 4983, 1985.

86. **Sheath, J., Grimwade, H. J., Waldron, K., Bickley, M., Taft, P., and Wood, C.,** Arteriovenous nonesterified fatty acids and glycerol differences in the umbilical cord at term and their relationship to fetal metabolism, *Am. J. Obstet. Gynecol.,* 113, 358, 1972.

87. **Szabo, A. J., Oppermann, W., Hanover, B., Gugliucci, C., and Szabo, O.,** Fetal adipose tissue development: relationship to maternal free fatty acid levels, in *Early Diabetes in Early Life,* Camerini-Davalos, R. A. and Cole, H. S., Eds., Academic Press, New York, 1975, 167.

88. **Knopp, R. H., Magee, M. S., Larson, M. P., and Benedetti, T.,** Alternative screening tests and birth weight associations in pregnant women with abnormal glucose screening, *Diabetes,* 37.(Suppl I), 110A, 1988.

89. **Skryten, A., Johnson, P., Samsioe, G., and Gustafson, A.,** Studies in diabetic pregnancy. II. Serum Lipids, *Acta Obstet. Gynecol. Scand.,* 55, 211, 1976.

90. **Lasuncion, M. A., Bonet, B., and Knopp, R. H.,** Mechanism of the HDL_2 stimulation of progesterone secretion in cultured placental trophoblast, *J. Lipid Res.,* 32, 1073, 1991.

91. **Winkel, G. A., Snyder, J. M., MacDonald, P. C., and Simpson, E. R.,** Regulation of cholesterol and progesterone synthesis in human placental cells in culture by serum lipoproteins, *Endocrinology,* 80, 1054, 1980.

92. **Cummings, S. W., Hatleey, W., Simpson, E. R., and Ohashi,** The binding of high and low density lipoproteins to human placental membrane fractions, *J. Clin. Endocrinol. Metab.,* 54, 903, 1982.

93. **Henson, M. C., Babischkin, J. S., Pepe, G. J., and Albrecht, E. D.,** Effect of the antiestrogen ethamoxytriphetol (MER-25) on placental low density lipoprotein uptake and degradation in baboons, *Endocrinology,* 122, 2019, 1988.

94. **Wu, Y. Q., Jorgensen, E. V., and Handwerger, S.,** High density lipoproteins stimulate placental lactogen release and adenosine 3',5'-monophosphate (cAMP) production in human trophoblast cells: evidence for cAMP as a second messenger in human placental lactogen release, *Endocrinology,* 123, 1879, 1988.

95. **Graham, D. L. and Oram, J. F.,** Characterization of a high density lipoprotein-binding protein in cell membranes by ligand blotting, *J. Biol. Chem.,* 262, 7439, 1987.

96. **Kern, F., Jr., Everson, G. T., DeMark, B., McKinley, C., Radene, S., Erfling, W., Braverman, D. Z., Szczepanik-Van Leeuwen, P., and Keline, P. D.,** Biliary lipids, bile acids, and gallbladder function in the human female, *J. Clin. Invest.,* 68, 1229, 1981.

97. **Knopp, R. H., Bergelin, R. O., Wahl, P. W., and Walden, C. E.,** Relationships of infant birth size to maternal lipoproteins, apoproteins, fuels, hormones, clinical chemistries and body weight at 36 weeks gestation, *Diabetes,* 34 (Suppl 2), 71, 1985.

98. Neville, M. C., Waxman, L. J., Jensen, D., and Eckel, R. H., Lipoprotein lipase in human milk: compartmentalization and effect of fasting, insulin, and glucose, *J. Lipid Res.*, 32, 251, 1991.

99. Jensen, D. R., Bessesen, D. H., Etienne, J., Eckel, R. H., and Neville, M. C., Distribution and source of lipoprotein lipase in mouse mammary gland, *J. Lipid Res.*, 32, 733, 1991.

100. Hachey, D. L., Thomas, M. R., Emken, E. A., Garza, C., Brown-Booth, L., Adlof, R. O., and Klein, P. D., Human lactation: maternal transfer of dietary triglycerides labeled with stable isotopes, *J. Lipid Res.*, 28, 1185, 1987.

101. Knopp, R. H., Walden, C. E., and Albers, J. J., Effect of postpartum lactation on lipoprotein lipids and apoproteins, *J. Clin. Endocrinol. Metab.*, 60, 542, 1985.

102. Knopp, R. H. and staff of the NW Lipid Research Clinic, What's new in the nutritional management of hyperlipidemia, in *Program Am. Dietetic Assoc. Annu. Meet.*, San Francisco, 1988, 14.

103. Montes, A., Walden, C. E., Knopp, R. H., Cheung, M., Chapman, M. B., and Albers, J. J., Physiologic and supraphysiologic increases in lipoprotein lipids and apoproteins in late pregnancy and postpartum: possible markers for the diagnosis of "pre-lipemia", *Arteriosclerosis*, 4, 407, 1984.

104. Glueck, C. J., Christopher, C., Tsang, R. C., and Mellies, M. J., Cholesterol-free diet and the physiologic hyperlipidemia of pregnancy in familial hypercholesterolemia, *Metabolism*, 29, 949, 1980.

105. McMurry, M. P., Connor, W. E., and Goplerud, C. P., The effects of dietary cholesterol upon the hypercholesterolemia of pregnancy, *Metabolism*, 30, 869, 1981.

106. Tsang, R. C., Glueck, C. J., McLain, C., Russell, P., Joyce, T., Bove, K., Mellies, M., and Steiner, P. M., Pregnancy, parturition, and lactation in familial homozygous hypercholesterolemia, *Metabolism*, 27, 823, 1978.

107. Hollingsworth, D. R. and Grundy, S. M., Pregnancy-associated hypertriglyceridemia in normal and diabetic women: differences in insulin dependent, non-insulin dependent and gestational diabetes, *Diabetes*, 31, 1092, 1982.

108. Knopp, R. H., Magee, M. S., Van Allen, M., McNealy, M., Walden, C. E., Larson, M. P., Plovie, B., Shiota, K., and Brown, Z., Placental cholesterol balance in IDDM pregnancy: implications for fetal growth, *Diabetes*, 38 (Suppl 2), 239A, 1989 (Abstr. #907)., *J. Reprod. Med.*, in press.

109. Bonet, B. J., Gown, A. M., Chait, A., and Knopp, R. H., Scavenger receptor activity in human placental cells, *Arterioscl. Thromb.*, 11, 1520a, 1991.

110. Rebourcet, R., Alsat, E., Mondon, F., Berthelier, M., Pastier, D., Cedard, L., Goldstein, S., and Polonovski, J., Detection of distinct receptors for native and acetylated low-density lipoproteins in human placental microvilli by ligand-immunoblotting, *Biochimie*, 68, 1135, 1986.

111. Malassine, A., Alsat, E., Besse, C., Rebourcet, R., and Cedard, L., Acetylated low density lipoprotein endocytosis by human syncytiotrophoblast in culture, *Placenta*, II, 191, 1990.

112. Mondon, F., Alsat, E., Berthelier, M., Rebourcet, R., Goldstein, S., and Polonovski, J., Presence of acetyl-like modified LDL in human placental blood, *Med. Sci. Res.*, 15, 385, 1987.