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Maternal and Umbilical Plasma Lipids Obtained During Elective Cesarean Section as Predictors of Macrosomia in Diabetic Pregnancy

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Abstract

MATERNAL AND UMBILICAL PLASMA LIPIDS OBTAINED DURING ELECTIVE CESAREAN SECTION AS PREDICTORS OF MACROSOMIA IN DIABETIC PREGNANCY

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Twenty-five pregnant women were recruited for this study as they presented for elective cesarean section at term. Comparison was made between 10 diabetic women and 15 nondiabetic women: 13 nondiabetic women with normal weight babies and six diabetic women with macrosomic babies. Radial artery, uterine vein, umbilical vein, and umbilical artery blood samples were analyzed in the fasting state for lipoprotein composition. Diabetic and diabetic-macrosomic infants had greater birth weight and skinfold measurements but not greater birth length.

It appears that higher triglyceride (TG) levels found in diabetics ($p=0.035$) are transferred to the fetus more efficiently ($p=0.009$) than in nondiabetics. Triglyceride levels however, did not correlate with skinfold measurements. Strong negative correlation was found between

skinfolds and both radial artery total cholesterol (r=-0.78; p=0.001) and HDL-C (r=-0.76; p=0.001).

KEYWORDS: diabetic pregnancy, macrosomia, umbilical plasma lipids, maternal plasma lipids.

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Each person whose signature appears below certifies that this manuscript in his/her opinion is adequate, in scope and quality, in lieu of a thesis for the degree Master of Science.

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Before the discovery of insulin in 1922, little was known about diabetic pregnancy. Most diabetic girls did not reach maturity. The few who did mature and conceive suffered high maternal and fetal losses (1). After the introduction of insulin, diabetic girls began to grow and mature normally. Their pregnancies however, were characterized by high fetal losses (2). After 1922 and until recently perinatal infant mortality and morbidity rates remained high at 20% to 50% (1). Complications included congenital anomalies, macrosomia (birth weight > 4,000 gms), birth injuries, respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia, and hyperinsulinemia (3).

Today "tight" control of maternal plasma glucose levels has been made possible by the introduction of new techniques for monitoring blood glucose levels at home, new methods of insulin delivery, and increased attention to dietary intake (1,4). Where this care and knowledge is available it has reduced the levels of perinatal infant mortality to 1-2%. This is similar to perinatal mortality in infants of nondiabetic pregnancies (5,6). In spite of excellent plasma glucose control, diabetic mothers continue to deliver macrosomic infants. It has been stated that macrosomia may be the result of other factors besides abnormal glucose metabolism in the diabetic pregnancy (7). Metzger et al.

(8) stated, "Our findings indicate that gestational diabetes is attended by disturbances of varying degrees in all major classes of insulin-dependent foodstuffs and must be viewed as a disorder of multiple fuels."

Little has been published on the relationship of maternal plasma lipoproteins to macrosomia in infants of diabetic mothers. This study was designed to compare maternal and cord lipids collected during elective cesarean section and their relation to fetal macrosomia in diabetic and nondiabetic pregnancy.

METHOD

All the following data were collected by Elmar Sakala, M.D., Division of Fetal and Maternal Medicine, Department of Gynecology and Obstetrics, Loma Linda University School of Medicine, and made available to me for statistical analysis.

Diabetic and nondiabetic pregnant women (n=25) were recruited for this study as they presented for elective cesarean section at term. Comparison was made between diabetic women (n=10) and nondiabetic women (n=15); and between nondiabetic women with normal weight babies (n=13) and diabetic women with macrosomic babies (n=6). The diabetic group included five Type 1, one Type 2, and four gestational diabetics.

Diabetic status was determined by standard criteria

Table 1. Inclusion criteria for subjects in study

1.	Gestational Age	38-40 weeks
2.	Mode of Delivery	Cesarean Section
3.	Anesthesia	Lumbar Epidural
4.	Labor	Absent
5.	Fasting State	NPO > 8 hours
6.	Time of Day	0800 - 1200 hours
7.	Intravenous Infusion	No Dextrose
8.	Tobacco Use	Nonsmoker

Statistical analyses included paired and grouped students' T-tests, chi square, analysis of variance and correlations.

RESULTS

No differences were found between diabetic and nondiabetic women, or between diabetics with macrosomic babies and nondiabetics with normal weight babies in the following parameters: age, parity, prepregnancy weight, body mass index (BMI), pregnancy weight gain (Table 2).

A higher incidence of male to female births was found in infants of diabetic mothers (4:1) compared with infants of nondiabetic mothers (3:2). No differences were found in ethnicity.

The infants of diabetic mothers were heavier ($p=0.001$) than infants of nondiabetic mothers (Table 3), but there was no difference in neonatal length. Mean skinfold measurements were higher in diabetic-macrosomic infants compared to nondiabetic-nonmacrosomic infants except for the suprailiac skinfold. Birth weight of diabetic and diabetic-macrosomic infants correlated with skinfold measurements with the strongest correlations found in diabetic-macrosomics: triceps ($r=0.81$; $p=0.001$), subscapular ($r=0.91$; $p=0.001$), suprailiac ($r=0.66$; $p=0.01$), and thigh ($r=0.70$; $p=0.01$).

Table 2. Age in years, parity, prepregnancy weight in kg, body mass index (BMI), pregnancy weight gain in kg in nondiabetic (NDM) and diabetic (DM) women; nondiabetic-nonmacrosomic (NDNMAC) and diabetic-macrosomic (DMAC) women (Mean ± SEM). No differences were found between any groups in these parameters.

	NDM n=15	DM n=10	p value	NDNMAC n=13	DMAC n=6	p value
Age in years	28.2±1.0	28.2±1.9	NS	29.1±1.1	27.3± 1.9	NS
Parity	2.1±0.2	1.4±0.5	NS	1.9±1.1	1.7± 0.7	NS
Prepregnancy Weight in Kg	*67.6±5.5	77.8±9.2	NS	†68.5±6.4	80.8±12.8	NS
BMI $\frac{\text{wt (kg)}}{\text{ht (m)}^2}$	*26.9±2.2	31.7±3.4	NS	†27.0±2.6	33.9± 5.4	NS
Pregnancy Weight Gain in Kg	*15.2±1.5	11.9±2.1	NS	†14.3±1.6	13.6± 3.0	NS

*n=14 †n=12

Table 3. Birth weight (BW), neonatal length (NLN) and skinfold measurements for triceps (TRI), subscapular (SUB), suprailiac (SUP), and thigh (THI) in infants of nondiabetic (NDM) and diabetic (DM) women; nondiabetic-nonmacrosomic (NDNMAC) and diabetic-macrosomic (DMAC) women (Mean ± SEM).

	NDM n=15	DM n=10	p value	NDNMAC n=13	DMAC n=6	p value
BW (gm)	3538.5±94.6	4139.6±144.1	p=0.001	3439.4±76.2	4437.7±112.1	p=0.000
NLN (cm)	52.2± 0.4	51.9± 0.9	NS	52.3± 0.5	53.0± 1.2	NS
TRI (mm)	4.0± 0.3	5.3± 0.5	p=0.046	3.6± 0.2	5.7± 0.6	p=0.001
SUB (mm)	3.4± 0.2	4.2± 0.5	NS	3.2± 0.1	4.8± 0.3	p=0.000
SUP (mm)	3.5± 0.3	3.8± 0.3	NS	3.2± 0.3	4.1± 0.5	NS
THI (mm)	5.2± 0.3	6.7± 0.1	p=0.000	5.1± 0.3	7.0± 0.0	p=0.000

Radial artery lipids correlated negatively with skinfold measurements (Table 4). Radial artery cholesterol was negatively correlated with subscapular ($r=-0.78$; $p=0.001$), suprailiac ($r=-0.62$; $p=0.014$), and triceps ($r=-0.59$; $p=0.022$) skinfolds. Radial artery HDL-C correlated negatively with suprailiac skinfold ($r=-0.76$; $p=0.001$). Radial artery TG and LDL-C did not correlate with any skinfold measurement. Thigh skinfolds were not influenced significantly by any lipid parameter.

No significant correlation was found between any plasma lipid and neonatal birth weight.

Absolute levels of radial artery TG (Figure 1) were higher in diabetic women as a group than in nondiabetic women ($p=0.035$). The mean TG (Figure 2) level was higher in radial artery than in uterine vein in diabetic women with macrosomic babies ($p=0.039$). This difference was not found in nondiabetic women with normal weight babies. The mean radial artery-uterine vein TG gradient was even more pronounced in diabetic-macrosomic compared to nondiabetic-nonmacrosomic women ($p=0.009$, Figure 3). Diabetic women with macrosomic babies not only had higher absolute levels of radial artery TG, but also greater gradients across the uterus. No difference was found in TG levels in the umbilical vein or artery between diabetic or macrosomic fetuses.

Table 4. Radial artery, total triglyceride (TG), total cholesterol (TC), HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C) in nondiabetic and diabetic women (n=15) correlated with triceps (TRI), subscapular (SUB), suprailiac (SUP), and thigh (THI) skinfold measures of their infants. Radial artery TC correlated with TRI, SUB, and SUP; HDL-C correlated with SUP.

	TG	TC	HDL-C	LDL-C
TRI	r=-0.35 NS	r=-0.59 p= 0.022	r=-0.39 NS	r=-0.20 NS
SUB	r=-0.20 NS	r=-0.78 p= 0.001	r=-0.33 NS	r=-0.05 NS
SUP	r=-0.16 NS	r=-0.62 p= 0.014	r=-0.76 p= 0.001	r=-0.12 NS
THI	r= 0.19 NS	r=-0.02 NS	r= 0.15 NS	r= 0.17 NS

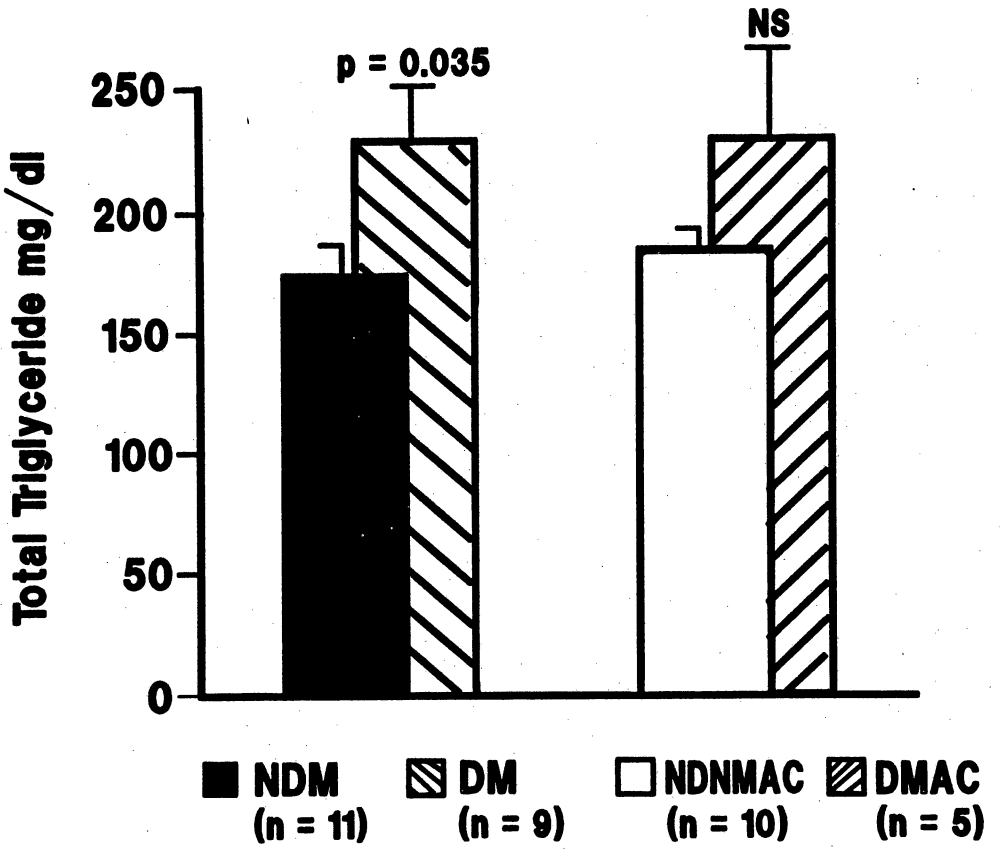

Figure 1. Comparison of total radial artery triglycerides in nondiabetic (NDM) and diabetic (DM); nondiabetic-nonmacrosomic (NDNMAC) and diabetic-macrosomic (DMAC) women (Mean±SEM). Total radial artery triglycerides were significantly greater in diabetic than in nondiabetic (p=0.035).

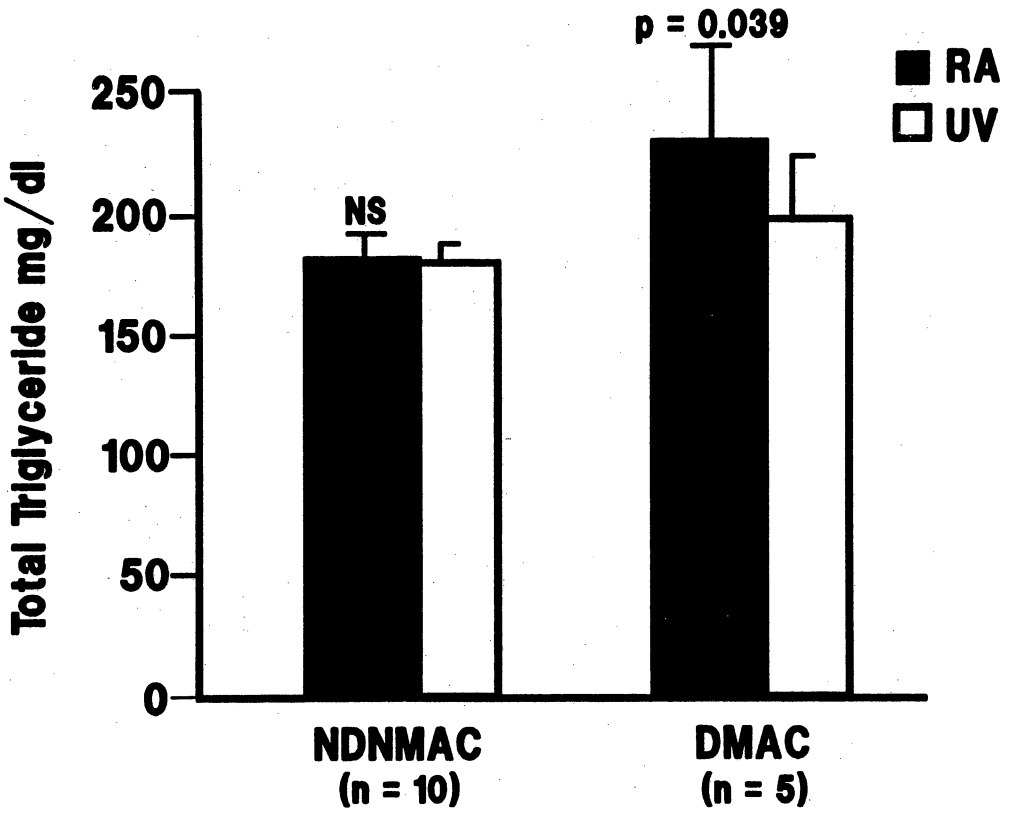

Figure 2. Total triglyceride from the radial artery (RA) and uterine vein (UV) in nondiabetic-nonmacrosomic (NDNMAC) and diabetic-macrosomic (DMAC) women (Mean±SEM). Mean TG level was greater in the RA than in the UV in DMAC (p=0.039).

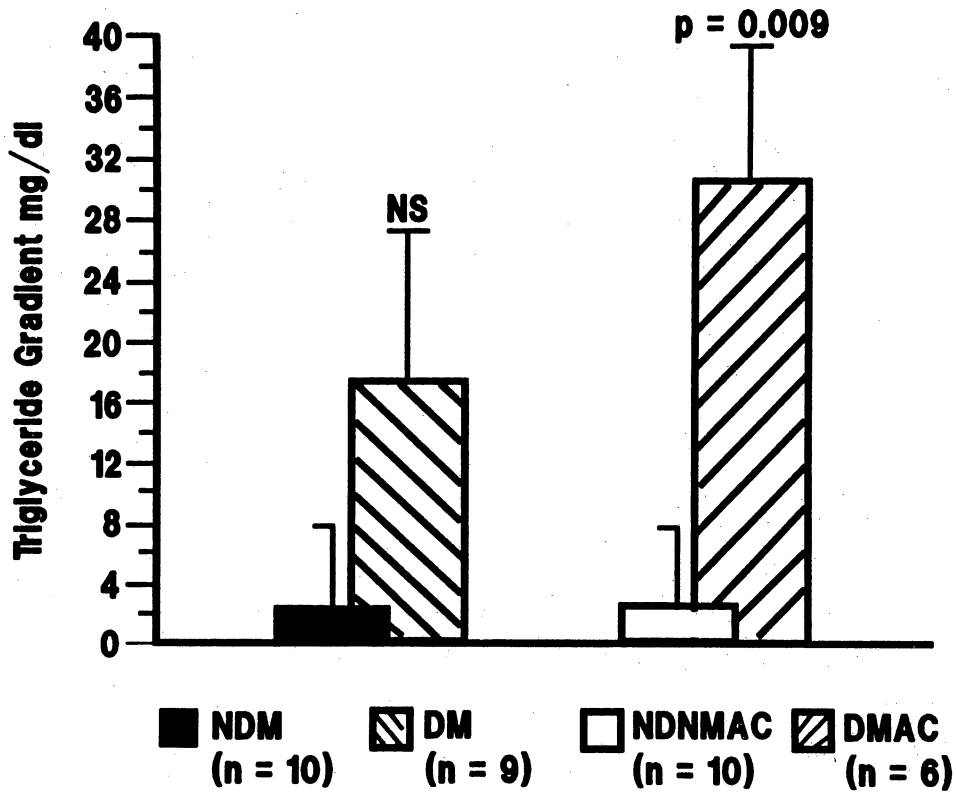

Figure 3. Triglyceride gradients from radial artery-uterine vein in nondiabetic (NDM) and diabetic (DM); nondiabetic-nonmacrosomic (NDNMAC) and diabetic-macrosomic (DMAC) women (Mean±SEM). DMAC radial artery-uterine vein gradients were greater than NDNMAC (p=0.009).

Nondiabetic women with normal weight babies had higher mean ratios (Figure 4) of total cholesterol to HDL-C in the radial artery than in the uterine vein ($p=0.014$). This difference was not found in diabetic women with macrosomic babies. This higher ratio was due to both increased total cholesterol and decreased HDL-C. However when total cholesterol and HDL-C were examined separately, no radial artery-uterine vein differences were seen.

When mean umbilical vein and umbilical artery values were compared (Table 5), both total cholesterol ($p=0.036$) and LDL-C ($p=0.043$) were found to be significantly higher in the umbilical vein in infants of diabetic women. These differences were not found in infants of nondiabetic women.

COMMENT

This study was designed to explore plasma lipids as predictors of macrosomia in as controlled a situation as is possible in a clinical setting. For this reason the inclusion criteria (Table 1) were more comprehensive than any previously reported in the literature. No difference was found (Table 2) between the groups in age, parity, prepregnancy weight, body mass index, pregnancy weight gain, or ethnicity, thus reducing the influence of confounding factors.

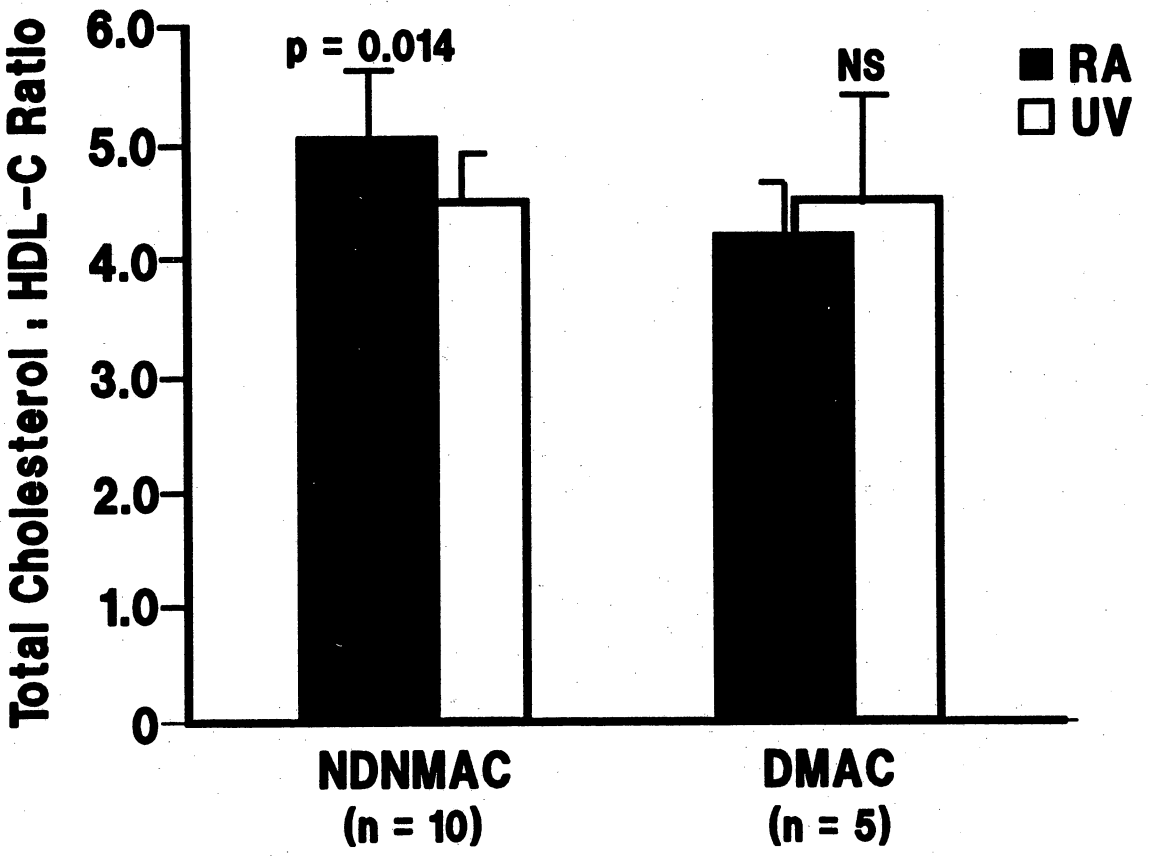

Figure 4. Total cholesterol (TC):HDL-cholesterol (HDL-C) ratio from the radial artery (RA) and the uterine vein (UV) in nondiabetic-nonmacrosomic (NDNMAC) and diabetic-macrosomic (DMAC) women (Mean±SEM). Ratio of TC:HDL-C was higher in the RA than in the UV in NDNMAC women (p=0.014).

Table 5. Total cholesterol and LDL-cholesterol in the umbilical vein (UMV) compared to the umbilical artery (UMA) in infants of nondiabetic (NDM) and diabetic (DM) women (Mean±SEM). UMV TC and LDL-C were higher (p=0.043; p=0.036) than UMA levels in DM women. This was not found in NDM women.

	TOTAL CHOLESTEROL			LDL-CHOLESTEROL		
	UMV	UMA	p value	UMV	UMA	p value
NDM (n=9)	70.3 ± 6.4	70.3 ± 6.1	NS	39.3 ± 3.0	39.0 ± 4.0	NS
DM (n=9)	72.8 ± 3.2	69.4 ± 3.2	p=0.036	42.8 ± 2.2	40.4 ± 1.8	p=0.043

The higher incidence of male to female births in the diabetic (4:1) compared to the nondiabetic (3:2) group was similar to reports by Fordyce (11) and Rovamo (12). It is not understood why the male:female sex ratio should be higher in diabetics. Even in gestational diabetes, where glucose intolerance is not manifest until the second trimester, a higher than normal male:female sex ratio was found (12).

The high correlation between birth weight and skinfold measurement (Table 3) without a significant increase in neonatal length indicated that our macrosomic infants were heavier because of increased adipose deposits and not increased length.

Increased TG levels (Figure 1) in diabetic women compared to nondiabetic women and increased TG arteriovenous gradients across the uterus (Figure 2) in diabetic women suggested that TG may play a part in macrosomic development in infants of diabetic mothers. The higher TG levels found in diabetic women appear to be efficiently transported across the placenta. It is possible that free fatty acid concentration may be increased due to the increased maternal TG concentration but also because of increased placental lipoprotein lipase activity (LPL). Biale (13) studying preeclampsia, suggested that stress caused by altered metabolic function may increase placental LPL activity. It

may be hypothesized that the stress of diabetic pregnancy increases LPL activity. Knopp (14) stated that human placental LPL activity did not decrease with the increased TG concentration found in diabetes. Increased activity of LPL will increase the concentration of free fatty acids crossing the placenta and could contribute to macrosomia.

Radial artery total cholesterol and HDL-C were inversely correlated with subscapular and suprailiac skinfold measurements respectively (Table 4). Radial artery cholesterol accounted for 61% ($p=0.001$) of the variation in subscapular skinfolds, 38% in suprailiac ($p=0.14$), and 35% in triceps ($p=0.22$). Radial artery HDL-C explained 57% ($p=0.001$) of the variation in suprailiac skinfolds. Our findings indicated that the lower the maternal total cholesterol and HDL-C levels, the higher the skinfold thicknesses. This appears in contrast to Knopp et al. (14), who suggested that increased maternal HDL-C levels may be associated with macrosomia because increased cholesterol levels are associated with increased steroid hormone production (15). The increased steroid hormones would result in increased overall size and not just increased adipose deposits, as was seen in our macrosomic babies. The increased radial artery TG levels found in the diabetic women compared to the nondiabetic did not correlate with skinfold measurements as we expected they would.

Why the radial artery total cholesterol:HDL-C ratio (Figure 4) should be higher than that found in the uterine vein of nondiabetic women with normal weight babies but not in diabetic women with macrosomic babies is not understood. The higher cholesterol levels in nondiabetic women with normal weight babies was also seen in the negative correlation of cholesterol with skinfold measures. These correlations were very strong and significant ($r=-0.78$; $p=0.001$).

This study found a significant correlation between neonatal skinfolds and birthweight. Cholesterol and HDL-C levels negatively correlated with skinfolds. Higher concentrations of maternal TG appeared to be available to the fetuses of diabetic and diabetic-macrosomic women. Control of maternal lipid levels may impact on fetal outcome. This study demonstrated the complexity of the subject and the need for more extensive research using larger numbers of subjects.

REFERENCES

1. Hollander P, Maeder EC. Diabetes in Pregnancy. Postgraduate Medicine 1985 77:(2)137-141, 144-146.

2. White P. Classification of Obstetric Diabetes. Am J Obstet Gynecol 1978 130:228-230.

3. Diamond MP, Salyer SL, Vaughn WK, Cotton RB, Entman SS, Roehm FH. Continuing Neonatal Morbidity in Infants of Women with Class A Diabetes. Southern Med J 1984 77(11):1386-1392.

4. Skyler JS. Control of Diabetes During Pregnancy: 1985. JAMA 1986 255:(5)647-468.

5. Freinkel N, Dooley SL, Metzger BE. Current Concepts Care of the Pregnant Woman with Insulin-Dependent Diabetes Mellitus. New Eng J Med 1985 313:(2)96-101.

6. Colwell JA, Horger ED, Mayfield RK, McFarland KF, Wheeler FC. Letter. New Eng J Med 1986 314:(1)59.

7. Kalkhoff RK. Therapeutic Results of Insulin Therapy in Gestational Diabetes Mellitus. Diabetes 1983:34 Suppl 2:97-100.

8. Metzger BE, Phelps RL, Freinkel N, Navickas IA. Effects of Gestational Diabetes on Diurnal Profiles of Plasma Glucose, Lipids, and Individual Amino Acids. Diabetes Care 1980 3:(3)402-409.

9. National Diabetes Data Group: Classification and Diagnosis of Diabetes Mellitus and Other Categories of Diabetic Intolerance. Diabetes 1979 28:1039-1057.

10. Valenzuela G, Harper MJK, Havashi RH. Uterine Venous, Peripheral Venous and Radial Arterial Levels of Prostaglandins E and F in Women with Pregnancy Induced Hypertension. Am J Obstet Gynecol 1983 145:11-14.

11. Fordyce MK, Duncan R, Chao R, Christakis M, Hsia SL, Robertson E, Kafatos A, Christakis G. Cord Blood Serum in Newborns of Diabetic Mothers. J Chron Dis 1983 36:(3)263-268.

12. Rovamo LM, Taskinen MR, Kuusi T, Raivio KO. Postheparin Plasma Lipoprotein and Hepatic Lipase Activities in Hyperinsulinemic Infants of Diabetic Mothers and in Large-for-Date Infants at Birth. Pediatric Research 1986 20:(6)527-531.

13. Biale Y. Lipolytic Activity in the Placentas of Chronically Deprived Fetuses. Acta Obstet Gynecol Scand 1985 64:111-114.

14. Knopp RH, Bergelin RO, Wahl PW, Walden CE. Relationships of Infant Birth Size to Maternal Lipoproteins, Apoproteins, Fuels, Hormones, Clinical Chemistries, and Body Weight at 36 Weeks Gestation. Diabetes 1985 34 Suppl 2:71-76.

15. Gwynne JT, Strauss JF. The Role of Lipoproteins in Steroidogenesis and Cholesterol Metabolism in Steroidogenic Glands. Endocr Rev 1982 3:299-329.