Relationships of Lipoprotein Lipids to Mild Fasting Hyperglycemia and Diabetes in Pregnancy

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The available data have been examined to determine if plasma lipids or lipoproteins are altered in pregnant subjects with adult-onset (type II) diabetes, gestational diabetes, or the hyperglycemic extreme of a randomly selected group of pregnant women attending a prepaid health plan. In each of these groups, a trend is observed toward an increase in total plasma and very low density lipoprotein triglycerides and a decrease in high density lipoprotein (HDL) cholesterol. These observations indicate that measurements of plasma triglyceride and HDL cholesterol may be valuable in identifying and quantifying the metabolic abnormality in gestational diabetes and in prognosticating fetal outcome. DIABETES CARE 3: 416–420, MAY–JUNE 1980.

The metabolism of both carbohydrates and lipids is altered in pregnancy as seen in changing plasma glucose and lipoprotein concentrations throughout gestation[1–4] (see ref. 1 for review). Because disorders of carbohydrate and lipid metabolism are often linked,[5,6] the question may be asked, Are plasma lipoprotein abnormalities more common in the diabetic pregnancy and in particular in the gestational diabetic pregnancy? An association of plasma lipid abnormalities with gestational diabetes is of potential interest on several accounts. Not all women identified as glucose intolerant in pregnancy are necessarily diabetic in the pathophysiologic sense or are destined to go on to develop overt diabetes.[7] Additional measurements to identify a truly pathophysiologic state and refine the diagnosis of gestational diabetes are therefore needed. Measurements of lipids in pregnancy may meet this need.

To date, little is known about lipoprotein lipid abnormalities in the diabetic pregnancy, particularly in gestational diabetes. Opinion in the existing literature is about evenly divided and only permits the conclusion that lipoprotein triglycerides are not necessarily elevated in diabetic pregnancy (see ref. 8 for review). A definitive answer to the question requires an epidemiologic study of normal, gestational diabetic, and overtly diabetic pregnant subjects of various classes originating from the same defined population. Such a study has not been performed. In the meantime, the available data need to be examined to determine if an association between hyperglycemia and lipoprotein abnormalities is likely. This is the focus of this report in which lipoprotein lipids are examined in various groups of diabetic or hyperglycemic subjects. Results are compared with gestationally age-matched controls, since gestational age is itself a crucial determinant of the degree of hyperlipidemia in pregnancy.[1–4]

METHODS

Subjects studied were drawn from three different populations. Normal or gestational diabetic subjects defined by the glucose tolerance test (GTT) criteria of O'Sullivan and Mahan[9] were studied at the Diabetes Clinic of the Boston City Hospital. The GTT was performed using 100 g oral glucose after a 3-day high carbohydrate diet.[8] Another group of subjects was studied while attending the Dystocia Clinic of the University Hospital, University of Washington Medical School. These subjects were either previously diabetic or newly recognized in pregnancy by virtue of fasting hyperglycemia or abnormal glucose tolerance testing again as judged by the criteria of O'Sullivan and Mahan.[9] A third group of subjects was drawn from a study of prospectively randomly selected pregnant women enrolled at a prepaid health plan, Group Health Cooperative of Puget Sound, and residing in a defined geographic area, i.e., King County. Further details of this study will be described in a later report. Results will be presented on the initial 350 cases examined from this study. Subjects were identified from a prenatal registration list, and 3 out of every 10 registrants were selected for study. Subjects then consenting to participate (about 70% of those invited) were seen in their homes by a nurse who drew blood after a

12–14-h overnight fast. Lipoprotein lipids were separated by ultracentrifugation at density 1.006 and heparin manganese precipitation as described in the Lipid Research Clinic's laboratory manual.[10] Aliquots of samples showing evidence of incomplete precipitation (i.e., turbidity) were reprecipitated after ultracentrifugation. Triglyceride and cholesterol were determined by using the AutoAnalyzer II technique.[10] Plasma glucoses were measured by the *o*-toluidine method.[11] Statistical comparisons employ Student's *t* test with prior $\log_{10}$ transformation of skewed triglyceride data.[8,12]

RESULTS

Observations in 38 normal, 22 gestational diabetic, and 10 overtly diabetic subjects studied at the Boston City Hospital Diabetes Clinic are presented in Table 1. It can be seen that plasma triglyceride concentrations are nearly identical in the normal and overtly diabetic pregnant subjects. Triglyceride concentrations are somewhat higher in the gestationally diabetic group, although this difference is not statistically significant. By contrast, plasma cholesterol concentrations tend to be higher in the overtly diabetic group. Gestational age is not significantly different in these three groups, but chronological age is significantly greater in the gestational diabetic group. The possibility that the tendency toward hypertriglyceridemia in these subjects is related to age cannot be excluded. In addition, a subset of gestational diabetic subjects in whom body weight measurements were obtained was heavier than the normal or overtly diabetic groups.[8]

The overtly diabetic subjects were not separated in this study according to type I (juvenile-onset) or type II (adult-onset) classifications. This distinction is important, since in nonpregnant subjects the two major diabetic classes show different lipoprotein abnormalities.[13,14] We have examined this question in a small group of pregnant diabetic subjects studied at various times in gestation. Shown in Table 2 are the means and standard errors for total plasma triglyceride concentrations in 12–22 serially studied normal subjects, type II, adult-onset diabetic subjects (White classes A and B), and type I, juvenile-onset diabetic subjects (classes C and below). The adult-onset diabetic subjects show higher mean triglyceride concentrations at all four gestational times. By contrast, type I subjects show no consistent difference from the normal subjects matched for gestational age. Measurements of high density lipoprotein (HDL) cholesterol in these same subjects are also presented at the four selected times. Compared with normal controls, the type II subjects have consistently lower HDL cholesterol concentrations (see individual data points plotted in Figure 1). By contrast, the type I subjects have HDL cholesterols that are little different from the normal control subjects. In these respects, plasma lipid changes in pregnancy appear to parallel those previously reported for the juvenile-onset versus adult-onset diabetic nonpregnant state.[13,14]

TABLE 1
Plasma triglyceride and cholesterol in normal and diabetic pregnancy

	Triglyceride (mg/dl)	Cholesterol (mg/dl)	Age (mg/dl)	Gestation (mg/dl)
Normal (38)	189 ± 58*	211 ± 28	26 ± 6	35 ± 3
Gestational diabetic subjects (22)	207 ± 110	209 ± 46	30 ± 5†	36 ± 4
Overt diabetic subjects (10)	180 ± 72	221 ± 29	29 ± 4	33 ± 4

Number of subjects in parentheses.
* Mean ± SD.
† Different from normal ($P < 0.02$).

TABLE 2
Total glycerides and HDL cholesterol in plasma of normal and adult- or juvenile-onset diabetic subjects in pregnancy

	Weeks of gestation			
	12	20	32	36
Triglyceride (mg/dl)				
Normal (12–22)	81 ± 8*	118 ± 10	178 ± 8	187 ± 10
Adult onset (1–5)	265	167	248 ± 27	223 ± 45
Juvenile onset (1–5)	76 ± 10	130 ± 22	138	174 ± 30
HDL cholesterol (mg/dl)				
Normal (12–22)	66 ± 4	77 ± 2	70 ± 3	65 ± 3
Adult onset (1–5)	43	49	50 ± 10	44 ± 5
Juvenile onset (1–5)	71 ± 12	68 ± 15	65	69 ± 3

Number of subjects in parentheses.
* Mean ± SE.

Similar differences are seen between a juvenile diabetic woman studied serially throughout gestation and a gestational diabetic* woman studied in late gestation (Table 3). Subject NS, a gestational diabetic woman, had a marked elevation in VLDL triglyceride at 32 wk gestation but returned to a below average level postpartum. In subject KC, a juvenile diabetic woman, VLDL triglyceride is average or somewhat above average antepartum, but falls again to a below average level postpartum. Thus, these subjects (and others in our experience as shown in Figure 1) have a reversible degree of hypertriglyceridemia due to the interaction of pregnancy and diabetes that cannot be attributed to diabetes or overt hypertriglyceridemia in the nonpregnant state. In the HDL fraction, cholesterol is generally above average in the juvenile diabetic subject and below average in the gestational diabetic subject. Interestingly, the HDL cholesterol concentration does not return to normal postpartum in subject NS or in the other type II subjects plotted in Figure 1, despite the fact that VLDL triglycerides are below average at this time.

To determine if the features of hypertriglyceridemia and low HDL cholesterol in this limited clinical sample extend to

*** The subject was not previously recognized as having diabetes and is therefore defined as a gestational diabetic woman. However, she had fasting hyperglycemia as well as glucose intolerance and was receiving insulin at the time of study.**

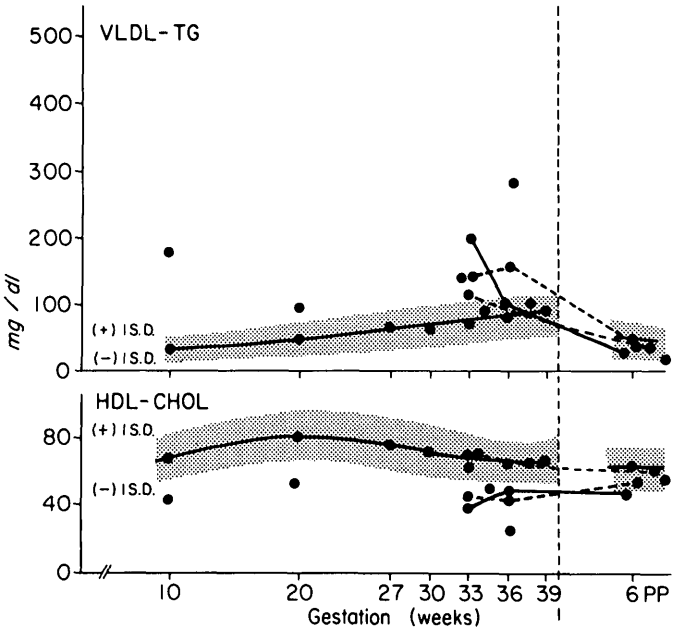

FIG. 1. VLDL triglyceride (TG) and HDL cholesterol (CHOL) concentrations in adult-onset (type II) diabetic subjects studied at various stages in pregnancy and 6 wk postpartum (PP). These subjects are compared with the mean ±1 SD (hatched area) for VLDL-TG and HDL-CHOL concentration for 12–22 serially studied normal pregnant subjects. Solid and dotted lines connect serially studied subjects.

mild fasting hyperglycemia in pregnancy, we have examined a data base of 350 prospectively randomly selected 36-wk gestation subjects attending the Group Health Cooperative of Puget Sound. The subjects were divided into two groups, separated by the 95th percentile for plasma glucose concentration at 36 wk gestation. Results are presented in Table 4. Twenty-three subjects were above the 95th percentile and 327 below. The prediction that hyperglycemic subjects would tend to have higher plasma triglyceride concentrations is fulfilled in these observations showing greater total and VLDL triglyceride concentrations. The HDL cholesterol concentration is not significantly lower. However, LDL cholesterol concentrations are significantly reduced. This reduction is not compensated for by an increase in VLDL cholesterol, which is 31.2 ± 1.1 in the normoglycemic group versus 35.4 ± 4.0 in the hyperglycemic group. As a result, total cholesterol tends to be lower in the hyperglycemic subjects: 250.1 ± 2.5 versus 235.0 ± 10.1. The 23 hyperglycemic subjects are also heavier and older than the nonhyperglycemic control subjects.

To further characterize the lipid changes associated with elevated fasting glucose, 6 subjects with the highest plasma glucose concentrations of the group of 350 are presented individually in Table 5. The subject with the highest plasma triglyceride concentration has the lowest HDL cholesterol and the highest glucose but is not the oldest or the heaviest. As a group, the 6 subjects with the highest plasma glucoses present a further upward trend in triglyceride concentration and body weight and a reduction in HDL cholesterol compared with the 23 subjects above the 95th percentile or the 327 normals. There is no further increment in age. Differences from the 327 normals are statistically significant for total and VLDL triglyceride and body weight. It may be con-

TABLE 4
Lipoprotein lipids, age, and body weight in 350 pregnant subjects above or below the 95th percentile for plasma glucose at 36 wk gestation

Plasma glucose*	<85 mg/dl (327)	>85 mg/dl (23)	P
Total triglyceride (mg/dl)	231.9 ± 87.7†	273.6 ± 110.0	<0.06
VLDL triglyceride (mg/dl)	123.7 ± 71.6	163.9 ± 93.1	<0.05
LDL cholesterol (mg/dl)	154.8 ± 43.2	135.8 ± 45.3	<0.05
HDL cholesterol (mg/dl)	64.1 ± 15.2	63.8 ± 12.8	NS
Age (yr)	27.6 ± 4.3	29.5 ± 3.6	<0.05
Maternal weight (kg)	75.1 ± 15.6	82.6 ± 14.8	<0.025

Number of subjects in parentheses.
* Glucose measured by the o-toluidine method.
† Mean ± SD.

TABLE 3
Serial lipoprotein lipid changes in pregnancy in normal, a gestional diabetic (NS), and a juvenile diabetic (KC) subject

	Weeks of gestation					
	Antepartum				Postpartum	
	12	20	32	36	6	20
VLDL triglyceride (mg/dl)						
Normal (12–22)	34 ± 4*	46 ± 7	71 ± 4	79 ± 7	43 ± 5	32 ± 4
NS	—	—	184	84	22	—
KC	34	79	—	136	19	29
HDL cholesterol (mg/dl)						
Normal (12–22)	66 ± 4	77 ± 2	70 ± 3	65 ± 3	—	—
NS	—	—	37	47	47	—
KC	99	96	—	68	82	65

* Mean ± SE.

TABLE 5
Lipoprotein lipids, glucose, age, and body weight in six subjects with the highest fasting glucose concentration in a random sample of 350 pregnancies

	Total TG* (mg/dl)	VLDL TG (mg/dl)	HDL C* (mg/dl)	Glucose (mg/dl)	Age (yr)	Weight (kg)
Subject						
1	277	141	73	92	27	84.0
2	215	121	62	106	25	122.0
3	191	107	68	91	33	94.5
4	310	201	62	95	33	99.0
5	546	401	48	111	28	88.0
6	366	256	51	94	29	60.0
Means						
Top 6	317.5	204.5	60.7	98.2	29.2	91.3
Top 23	273.6	163.9	63.8	—	29.5	82.6
Bottom 327	231.9	123.7	64.1	—	27.6	75.1
P (6 vs. 327)	<0.05	<0.02	NS	—	NS	<0.02

* TG, triglyceride; C, cholesterol.

cluded from these data that elevated fasting glucose concentrations are associated with increases in plasma total and VLDL triglyceride concentrations and body weight and to a lesser extent greater age. Of interest is the fact that infant weight ranged from 3200 to 4644 g in these subjects. None of the 6 was recognized as clinically having diabetes but one had a positive family history of diabetes.

DISCUSSION

We have attempted to determine if elevated plasma triglycerides and a reduced HDL cholesterol are likely to occur more frequently in subjects with mild fasting hyperglycemia, gestational diabetes, or adult-onset (type II) diabetes mellitus. In each group examined greater triglyceride concentrations, body weight, chronological age, and lower HDL cholesterol are repeatedly associated. Therefore, the data strengthen the likelihood that plasma lipid abnormalities are more common in mild or gestational diabetes in pregnancy.

Limitations in interpreting these data and previously published reports[8,15] require mention. The number of subjects studied is limited. In addition, it has not been established in any of the studies done that the nondiabetic and diabetic subjects are drawn from the same defined population. Only in the data presented in Tables 4 and 5 is there certainty that the normoglycemic versus hyperglycemic subjects are in fact drawn from the same population, i.e., a prospectively selected sample of pregnant women enrolled in a prepaid health plan and residing in a defined geographical area. The association of hypertriglyceridemia, hyperglycemia, and increased body weight is particularly striking in these data. Whether or not the same relationships exist in a group of gestational diabetic subjects requires further study, since GTTs were not performed in our study sample and clinical experience indicates that pregnant women with fasting hyperglycemia may not always be glucose intolerant.

The data presented are sufficient to justify further investigation of the association between hypertriglyceridemia, reduced HDL cholesterol concentrations, obesity, and gestational diabetes. Quantifying these associations could refine the ability to diagnose the metabolic abnormality in gestational diabetes, since any single test is inevitably associated with false positive and false negative results.

If the pathophysiologic significance of hypertriglyceridemia in diabetic pregnancy were known, this information would also be of value in deciding whether lipid testing would be helpful in diagnosis and monitoring of the gestational diabetic woman. Unfortunately, this information is also not available. However, studies in the nondiabetic pregnant rat model show that an increased entry of endogenous triglycerides into the circulation is the primary cause for the hypertriglyceridemia of pregnancy.[16,17] In the obese type II diabetic pregnancy increased insulin secretion in association with obesity could augment hepatic triglyceride production. On the other hand, insulin resistance or insulin deficiency itself could be associated with deficient lipoprotein lipase-mediated triglyceride removal by a number of tissues. Whichever mechanisms are operative, Skryten et al.[15] have already reported a positive association between plasma triglycerides and infant weight in diabetic pregnancy. In this regard it remains to be seen if the degree of hypertriglyceridemia reflects the lack of diabetic control or if free fatty acids or triglyceride fatty acids contribute directly to the excessive adiposity of the infant of the diabetic mother.

We conclude that the available data justify further investigation of the frequency of lipoprotein abnormalities in carefully defined populations of normal and diabetic subjects, their relationship to hyperglycemia, and the potential value of lipoprotein abnormalities in refining diagnosis and prognosis in gestational diabetes.

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