THE DIABETIC PREGNANCY

A STUDY OF SERUM LIPIDS IN MATERNAL AND UMBILICAL CORD BLOOD AND OF THE UTERINE AND PLACENTAL VASCULATURE

BY

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It has been shown that even with good diabetic control foetal loss in diabetic pregnancy exceeds the standard (Farquhar, 1959; Hagbard, 1961; Oakley, 1961).

There is now evidence that in the non-diabetic an increase in the low-density serum lipoproteins plays a part in the causation of degenerative vascular disease (Gofman, Jones, Lindgren, Lyon, Elliott and Strisower, 1950; Kannel, Dawber, Kagan, Revotskie and Stokes, 1961). It has also been shown that in diabetes there is a tendency for these low-density lipoproteins to be increased, particularly in the untreated or poorly controlled patient (Albrink and Man, 1958; Wolff and Salt, 1958; Salt, Wolff, Nestadt and Lloyd, 1960), but it is not clear whether this lipidaemia is important in the causation of the vascular complications of diabetes. In normal pregnancy a considerable rise of low-density lipoproteins occurs and reaches its peak during the last trimester (Oliver and Boyd, 1955; Studnitz, 1955; Watson, 1957; Smith, de Alvarez and Forsander, 1959; de Alvarez, Gaiser, Simkins, Smith and Bratvold, 1959). We present a study designed to show whether: (1) in diabetic pregnancy this rise in serum lipoproteins is more marked and/or occurs at an earlier stage of pregnancy; (2) the lipids in umbilical cord blood of infants of diabetic mothers differ from those of infants of non-diabetic mothers; and (3) a correlation exists between increased concentrations of lipoproteins on the one hand, and the state of the blood vessels in the rectus muscle, uterus, and placenta, and the outcome of pregnancy on the other.

Patients and Methods

We have studied 48 non-selected pregnant diabetic women, 4 'potential diabetic' ('pre-diabetic') pregnant women, and, for comparison, 21 non-diabetic pregnant women. Table 1 gives the age, duration of diabetes, and occurrence of diabetic complications: 7 patients had as their only finding an abnormal glucose tolerance test (blood sugar determined by the method of Hoffman (1937) greater than 180 mg./100 ml. at one hour and greater than 120 mg./100 ml. at two hours) which was done because of a suggestive history. 'Potential diabetes' was diagnosed in 4 patients with a normal glucose tolerance test and a history of at least two of the following: previous infant with birth weight over 10 lb. (4.5 kg.), unexplained stillbirth, hydramnios without foetal abnormality, and a positive first-degree family history of diabetes. The non-diabetic pregnant women, studied for comparison, were booked for hospital delivery and attended the antenatal clinic. This group included patients in whom an obstetrical complication was present or anticipated, but none with a positive first-degree family history of diabetes or with vascular or renal disease. Table 2 summarizes the obstetrical histories.

The diabetic and 'potential diabetic' patients attended a special antenatal clinic at weekly intervals and were admitted to hospital between the 32nd and 34th week of pregnancy for rest and even closer medical supervision. In the majority of cases delivery was carried out between the 36th and 38th week of gestation by lower segment caesarean section. Quality of diabetic control during pregnancy, changes in insulin requirements, time and mode of delivery, and the outcome of the pregnancy are presented in Table 3. For the assessment of diabetic control the following criteria have been used: *Good*: no ketosis; no diabetic symptoms; infrequent hypoglycaemia; and average blood sugar two hours after a meal less than 180 mg./100 ml. *Fair*: no ketosis; no diabetic symptoms; infrequent hypoglycaemia; and average blood sugar two hours after a meal between 180 and 250 mg./100 ml. *Poor*: ketonuria at times; diabetic symptoms

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TABLE 1
AGE OF PREGNANT WOMEN AND DURATION AND COMPLICATIONS OF DIABETES

	No.	Age (yr.) (mean and range)	Duration of Diabetes		Diabetic Complications	
			< 10 yr.	> 10 yr.	Retinopathy	Nephropathy
Diabetic women (48)						
On insulin	33	27 (19-38)	21	12	2	1
On chlorpropamide .. .	2	37 (35-40)	2	—	—	—
On diet alone .. .	6	37 (32-40)	4	2	—	—
'Glucose tolerance test diabetic' ..	7	33 (27-41)	—	—	—	—
'Potential diabetic' women .. .	4	32 (25-38)	—	—	—	—
Non-diabetic women .. .	21	30 (17-42)	—	—	—	—

TABLE 2
OBSTETRIC HISTORY AND FAMILY HISTORY OF DIABETES

	No.	Parity					Past Obstetric History			First Degree Family History of Diabetes
		0	1	2	3	4 and over	Abortions	Stillbirths and Neonatal Deaths	Infants with Birth Weight over 10 lb. (4.5 kg.)	
Diabetic women										
On insulin .. .	33	13	11	6	2	1	7	6	3	12
On chlorpropamide .. .	2	—	2	—	—	—	1	—	—	1
On diet alone .. .	6	—	—	1	—	5	3	2	2	3
'Glucose tolerance test diabetic' ..	7	—	3	2	2	—	4	1	1	2
'Potential diabetic' women .. .	4	—	1	1	—	—	2	1	2	2
Non-diabetic women .. .	21	5	5	5	2	4	7	6	—	—

present; frequent hypoglycaemia; and average blood sugar two hours after a meal more than 250 mg./100 ml. Our one case of 'poor' control was thus classified because of a single episode of ketosis. She developed acute appendicitis and was operated on at the 27th week of pregnancy. She was delivered at 35½ weeks and her infant died 14 hours after birth. Pre-eclampsia was not seen in the diabetic patients. Pregnancies resulting in abortion, intrauterine death, neonatal death, or an infant with severe respiratory distress syndrome were not associated with unsatisfactory control, marked increase in insulin requirement, long duration of diabetes, or the presence of diabetic complications. The abortion rate of 10% is in agreement with many other reports (Hagbard, 1961; Koller, 1953; Pedowitz and Shlevin, 1955). The over-all loss of viable foetuses was 6%. In both patients treated with chlorpropamide the pregnancy resulted in foetal death at 26 weeks.

Serum lipoproteins were estimated at monthly intervals in the diabetic and 'potential diabetic' women, and one to four times during pregnancy in the non-diabetic women. Venous blood was collected between 10 and 11 a.m. and, to minimize the effect of alimentary lipaemia, the serum was centrifuged for 30 minutes at 10,000 × g and the chylomicron layer discarded. Serum total lipid was estimated, before and after removal of the chylomicra, by the method of de la Huerza, Yesinick and Popper (1953); total cholesterol by the method of Sackett (1925); and

phospholipid (lipid phosphorus × 26) by a method adapted from Gomori (1942). Lipoproteins were determined by paper electrophoresis (Salt and Wolff, 1957).

In addition the following investigations were carried out on sub-groups for which neither patients nor controls were specially selected.

1. Total lipid, cholesterol, and phospholipid were estimated in the cord blood (serum) of 28 infants of the diabetic mothers, in 3 infants of the 'potential diabetic' mothers, and in 5 infants of non-diabetic mothers. In the estimation of cholesterol no correction was made for bilirubinaemia. Using the method of Sackett (1925), Mortimer (1964) found that 1 mg./100 ml. of unconjugated bilirubin gives a positive error of about 4 mg./100 ml. in the cholesterol determination. Cord bilirubin levels, except in haemolytic disease, rarely exceed 2-3 mg./100 ml.

2. Biopsy specimens were obtained from the rectus muscle and uterus at the time of caesarean section in one 'potential diabetic' and 23 diabetic patients, and, for comparison, similar specimens were obtained from 10 non-diabetic women requiring this operation. Frozen and paraffin sections were made and stained with haematoxylin and eosin, elastin-van Gieson, and periodic acid-Schiff before and after digestion with diastase.

3. The placentas of 23 diabetic and 3 'potential

TABLE
DIABETIC CONTROL AND OUTCOME OF PREGNANCY

	No.	Diabetic Control			Insulin Requirements During Pregnancy								
		Good	Fair	Poor	1st-12th Week			13th-24th Week			25th Week Delivery		
					Up	Same	Down	Up	Same	Down	Up	Same	Down
Diabetic women													
On insulin	33	15	17	1	10	20	3	24	3	4	28	1	
On chlorpropamide	2	2	—	—									
On diet alone	6	5	1	—									
'Glucose tolerance test diabetic'	7	—	—	—									
'Potential diabetic'	4	—	—	—									
Total	52												

* Abortions and intrauterine deaths are not included.

diabetic' patients were examined by similar methods. Because most of the diabetic women were delivered before the 38th week of gestation it was impossible to obtain satisfactory control material; however several placentas from non-diabetic women delivered before term were examined.

4. In 10 of the diabetic patients a further study of the placental vasculature was made by radiological examination after the injection of barium into the umbilical vein and a similar study was made of 11 placentas from non-diabetic women delivered at term. The placentas were received unfixed and examined as soon as possible after delivery, usually within 24 hours. After external examination, they were immersed in warm (40-50° C.) normal saline preparatory to injection and kept immersed during this procedure, the saline being changed as necessary to maintain the temperature. The umbilical vein was cannulated and any air bubbles were allowed to escape. The vein was flushed through with warm normal saline for 15 to 20 minutes until a clear flow from the maternal surface was observed. The saline was then replaced by an 80% suspension of barium sulphate* in gelatin, at a similar temperature, for a period of three minutes. The injection force was supplied by compressed air at a pressure of 150 mm. Hg. The placenta was x-rayed after fixation in 10% formol saline.

Results

Table 4 shows the serum lipoprotein levels (after removal of chylomicron material) at intervals during pregnancy. The amount of chylomicron material did not exceed the normal in any of the patients or controls. Patients not requiring insulin, i.e. patients treated with diet alone or with chlorpropamide, those in whom the only abnormality was impaired glucose tolerance, and 'potential diabetics' are grouped together; these groups did not differ significantly from each other in respect of their lipoprotein levels. Between the 12th and 16th weeks of pregnancy the mean concentrations of total lipid,

total cholesterol, phospholipid, and α -lipoprotein lipid were somewhat higher in the diabetic than in the non-diabetic group, though for cholesterol this finding only applies to patients treated with insulin. Only in the case of α -lipoprotein did the difference reach statistical significance ($t = 3.77$, $p = 0.001$). Though the mean β -lipoprotein lipid was not raised, inspection of the electrophoretic strips showed even at this early stage of pregnancy a marked pre- β band in five of the diabetic, but in none of the non-diabetic, patients. From the 16th week of pregnancy onwards no difference was found between the diabetic and non-diabetic women in total lipid, cholesterol, phospholipid, β -lipoprotein, and pre- β -lipoprotein, all of which increased steadily. α -Lipoprotein increased in the non-diabetic women between the 16th and 32nd weeks of pregnancy and reached levels similar to those in the diabetic women; the latter maintained the raised levels already present before the 16th week. After the 32nd week α -lipoprotein concentrations decreased in the non-diabetic, but remained raised in the diabetic patients; at this stage the difference between the mean levels in the insulin-treated diabetic and the non-diabetic women once more became significant ($t = 2.1$, $p < 0.05$).

Analysis of these data showed no correlation between increases of the various lipoprotein fractions on the one hand and the incidence of intrauterine death, neonatal death, and the pulmonary distress syndrome in the newborn on the other.

Table 5 shows the serum lipid levels in cord blood. The mean values for cholesterol and phospholipid were higher in infants of diabetic than of non-diabetic mothers. The difference between the levels in the infants whose mothers had not had insulin and the controls was highly significant for cholesterol ($t = 3.6$, $p 0.001$) and phospholipid ($t = 3.4$, $p 0.001$). The difference between the levels in the infants whose mothers had insulin during pregnancy and the controls was less marked (for

* 'Micropaque', Demancy & Co. Ltd.

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IN 52 PATIENTS INCLUDING 4 'POTENTIAL DIABETICS'

Gestation at Delivery* (wk.)					Mode of Delivery*		Abor- tions	Intra- uterine Deaths	Neonatal Deaths	Appearance of Infant at Birth		Pulmonary Distress Syndrome		
35	36	37	38	39	Caesar- ean Section	Vaginal				Normal	'Diab- etic'	Absent	Mild	Severe
2	12	8	7	1	27	3	3	—	3	12	18	18	5	7
—	2	4	—	—	3	3	2	—	—	1	5	5	1	—
—	3	1	3	—	4	3	—	—	—	5	2	7	—	—
—	—	2	2	—	3	1	—	—	—	4	—	4	—	—
2	17	15	12	1	37	10	5	—	3	22	25	34	6	7

phospholipid $t = 2.5$, $p < 0.02$; for cholesterol $t = 1.8$, $p > 0.05$). The cholesterol levels in infants of diabetic mothers who did not receive insulin were significantly higher than in those whose mothers received insulin ($t = 2.4$, $p < 0.02$); in the case of phospholipid the difference was not significant ($t = 1.9$, $p > 0.05$).

The only abnormal biopsy from the rectus muscle

was that of a non-diabetic patient showing medial hypertrophy of the arteries. In 12 of the 24 diabetic and 6 of the 10 non-diabetic women, biopsies from the uterus showed a variety of vascular changes: 4 of the diabetic and 1 of the non-diabetic patients had minor abnormalities of the endometrial sinusoids (mural thrombi, intramural haemorrhage, and deposits of PAS-positive material), and a similar

TABLE 4
SERUM LIPID LEVELS (means in mg./100 mL) AT VARIOUS STAGES OF PREGNANCY

		Weeks of Pregnancy					
		12-16	17-20	21-24	25-28	29-32	33-Delivery
Total lipid	Diabetic women on insulin	828 (115) 25	832 (135) 19	898 (140) 24	1,007 (176) 27	1,108 (266) 29	1,083 (205) 26
	Diabetic women not on insulin and 'potential diabetics'	830 (170) 2	890 (116) 5	886 (60) 5	1,068 (115) 11	1,094 (117) 16	1,168 (112) 16
	Non-diabetic women	748 (164) 10	1,002 (145) 5	957 (137) 8	958 (103) 6	1,167 (165) 4	1,123 (197) 12
Total cholesterol	Diabetic women on insulin	252 (51) 25	264 (59) 19	289 (75) 24	292 (70) 27	296 (62) 29	306 (63) 26
	Diabetic women not on insulin and 'potential diabetics'	220 (4) 2	245 (6) 5	248 (24) 5	298 (48) 11	287 (50) 16	298 (30) 16
	Non-diabetic women	225 (37) 10	256 (38) 5	276 (33) 8	255 (19) 6	337 (74) 5	321 (72) 11
Phospholipid	Diabetic women on insulin	299 (70) 25	312 (72) 19	332 (64) 24	344 (69) 27	357 (68) 29	368 (75) 25
	Diabetic women not on insulin and 'potential diabetics'	315 (88) 2	305 (30) 5	340 (31) 5	374 (62) 11	358 (58) 16	370 (35) 16
	Non-diabetic women	276 (41) 9	344 (77) 5	317 (52) 8	321 (33) 6	393 (38) 5	355 (66) 11
β -lipoprotein lipid	Diabetic women on insulin	417 (94) 25	450 (128) 19	492 (146) 24	607 (181) 27	717 (337) 29	693 (189) 26
	Diabetic women not on insulin and 'potential diabetics'	482 (124) 2	491 (108) 5	500 (67) 5	682 (109) 11	697 (162) 16	768 (106) 16
	Non-diabetic women	434 (159) 10	572 (204) 5	535 (129) 8	577 (74) 6	751 (206) 4	745 (203) 12
α -lipoprotein lipid	Diabetic women on insulin	336 (85) 25	303 (59) 19	317 (68) 24	308 (68) 27	302 (55) 29	298 (51) 26
	Diabetic women not on insulin and 'potential diabetics'	363 (14) 2	319 (28) 5	332 (64) 5	292 (55) 11	287 (51) 16	288 (60) 16
	Non-diabetic women	241 (58) 10	343 (71) 5	315 (44) 8	294 (67) 6	300 (71) 4	261 (50) 12
β/α ratio	Diabetic women on insulin	1.4 (0.6) 25	1.6 (0.6) 19	1.7 (0.8) 24	2.1 (0.9) 27	2.5 (1.3) 29	2.4 (0.9) 26
	Diabetic women not on insulin and 'potential diabetics'	1.9 (0.4) 2	1.6 (0.9) 5	1.6 (0.9) 5	2.5 (0.7) 11	2.6 (1.0) 16	2.7 (0.9) 16
	Non-diabetic women	1.9 (0.8) 10	1.8 (0.9) 5	1.7 (0.4) 8	2.1 (0.7) 6	2.9 (1.2) 5	3.0 (1.2) 12

Standard deviations in brackets.

Number of observations in italics.

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TABLE 5
SERUM LIPID LEVELS IN CORD BLOOD

	No.	Serum Lipids (mg. 100 ml., means and standard deviations)		
		Total Lipid	Cholesterol	Phospholipid
Infants of:				
Diabetic women treated with insulin	20	275 (89)	83 (23)	128 (25)
*Diabetic women not treated with insulin	11	365 (134)	110 (30)	155 (46)
Non-diabetic women	5	286 (76)	71 (13)	94 (26)

* 3 'potential diabetics', 5 'glucose tolerance test' diabetics, and 3 diabetics on diet alone.

proportion of both groups showed intimal thickening due to proliferation or hydropic vacuolation of endothelial cells. Five of the diabetic and 3 of the non-diabetic specimens showed fibrous and elastic thickening of the arterial walls. Fatty change was present in 2 of the diabetic specimens: in 1 the lipid was in the media and in the other it involved the

endothelial cells. In these 2 patients the serum β -lipoprotein levels towards the end of pregnancy were higher (997 and 905 mg./100 ml.) than in the other diabetic patients (mean value 655 mg./100 ml.; range 458-854 mg./100 ml.). Fatty change was not seen in any of the non-diabetic biopsies.

The placentas from the diabetic patients showed

FIG. 1.—Radiograph of placenta, injected with barium, showing a focal filling defect.

TABLE 6
SERUM LIPID LEVELS IN DIABETIC PATIENTS AT THE END OF PREGNANCY
CORRELATED WITH RADIOGRAPHIC APPEARANCES OF PLACENTA

Placental Radiographic Appearances	No.	Serum Lipids (mg./100 ml., means and standard deviations)					
		Total Lipid	Cholesterol	Phospholipid	β -Lipoprotein Lipid	α -Lipoprotein Lipid	β/α Ratio
Normal	5	1,182 (167)	332 (110)	376 (60)	771 (153)	312 (22)	2.48 (0.42)
Focal filling defects	5	1,376 (212)	344 (66)	383 (47)	983 (210)	285 (44)	3.54 (1.07)

small infarcts in 14 out of the 26 examined, a similar proportion to that observed in the non-diabetics. Histological assessment of the placental vessels proved difficult. Those in the normal placenta have a prominent endothelial lining, no elastic laminae, and a thick media. There is a considerable range of normal appearances and no distinctive features were seen in the diabetic placentas. The general architecture of the villi was normal, but syncytial knots tended to be more numerous and larger in the diabetic placentas. Only 3 of the diabetic placentas were judged to be completely normal, and in these women the serum levels of total lipid (1,020, 990, and 940 mg./100 ml.) and β -lipoprotein (627, 717, and 413 mg./100 ml.) in later pregnancy were somewhat lower than the mean levels in those whose placentas showed some histological abnormality (total lipid 1,150 mg./100 ml., range 910-1,290 mg./100 ml.; β -lipoprotein 751 mg./100 ml., range 458-1,109 mg./100 ml.).

In 5 out of 10 placentas from diabetic and 8 out of 11 from non-diabetic patients the radiographs showed no abnormalities. In 3 diabetic and 3 non-diabetic specimens there was defective filling of the vessels of part of the placenta (Fig. 1). In the remaining 2 diabetic placentas the changes were similar but less marked. Table 6 shows the levels of serum lipids in diabetic patients towards the end of pregnancy correlated with the radiographic appearances of the placentas. The mean values for total lipid, cholesterol, phospholipid, β -lipoprotein, and the β/α ratio were higher in patients whose placentas showed focal filling defects than in those with normal filling. This difference was most marked in the case of β -lipoprotein and the β/α ratio, though in this small series statistical significance was not reached (for β -lipoprotein $t = 1.76$, $p > 0.1$; for the β/α ratio $t = 2.1$, $p > 0.05$).

Discussion

Ditzel and Moinat (1957) and Vernet and Smith (1961) have studied the serum lipoproteins in pregnant diabetic women. The former found that large fluctuations in lipoproteins occurred throughout

pregnancy, and they could often relate these fluctuations to poor diabetic control. We did not encounter such fluctuations; in fact, a striking feature in the women who, early in pregnancy, showed high total lipid levels and the presence of a marked pre- β band was the constancy of these findings. In our patients diabetic control was with one exception good or at least fair, and this fact probably explains why we are unable to confirm Ditzel and Moinat's findings. Vernet and Smith also found differences in certain lipid fractions between normal and diabetic pregnant women. Cholesterol levels were higher, and a marked pre- β -lipoprotein fraction was present at an earlier stage of pregnancy in the diabetic group. In a small proportion of our patients (5 out of 52) we made the same observation, though, taking our diabetic group as a whole, we were unable to find any significant differences from the non-diabetic group in cholesterol or the pre- β -lipoprotein fraction at any stage of pregnancy. Possibly a difference in the age distribution between the patients of Vernet and Smith and our patients may explain why our findings are at slight variance with theirs, our non-diabetic group having a higher mean age than theirs (30 and 26.5 years respectively). With advancing age serum lipoprotein levels tend to rise, and in a more detailed study of pre- β -lipoprotein we have shown (Pantelakis, Fosbrooke, Lloyd and Wolff, 1964) that at all stages of pregnancy diabetic and non-diabetic women over 30 years of age have a higher incidence of this fraction than those under 30.

In our studies of primary and secondary disturbances of lipid metabolism we have not previously encountered increases in α -lipoprotein. Our finding of significantly higher levels of α -lipoprotein in the diabetic patients during the early months of pregnancy and after the 32nd week requires confirmation.

Recently Lloyd (1963) and Mortimer (1964) studied cord serum lipids in infants of diabetic mothers and found that the mean levels of cholesterol were higher than those in infants of non-diabetic mothers; but in their series there was no difference between the phospholipid levels, and their investigations did not include infants of diabetic mothers not receiving insulin. At present we can only speculate

about the reason for the higher lipid levels in the cord blood of infants of diabetic mothers. In infants of normal mothers cord blood lipoproteins do not vary with the level of maternal lipids, the maturity of the infant, or the birth weight (Rafstedt, 1955), and we have made the same observations for infants of diabetic mothers. Though it is known that the large lipoprotein molecules do not cross the placental barrier in significant amounts, there is evidence that in the rat non-esterified fatty acid (NEFA) crosses the placenta (Goldwater and Stetten, 1947), and that in the human it readily diffuses across vascular membranes (Fredrickson and Gordon, 1958). NEFA is increased in untreated diabetes and even with good control NEFA concentrations are likely to be higher than in the non-diabetic, at least for periods in the day. Conceivably the relatively high level of cholesterol in the cord blood of the infants of diabetic mothers results from passage of maternal NEFA across the placenta and subsequent synthesis of large lipoprotein molecules. The even higher concentrations of cholesterol and phospholipid in the infants of the diabetic mothers not receiving insulin may be the result of higher levels of NEFA in these women. Studies of NEFA concentrations in diabetic pregnancy and in cord blood are needed to confirm these speculations.

Reis, DeCosta, and Allweiss (1950) examined diabetic placentas by light microscopy and did not discover significant abnormalities. Burstein, Soule, and Blumenthal (1957) made detailed studies of the placentas from normal pregnancies, in hypertensive and toxæmic states, and in diabetes. They report that the majority of diabetic placentas show cellular proliferation and deposition of P.A.S. positive material in the intima and consider this change to be specifically related to diabetes. Our histological studies showed no changes that were not also seen in non-diabetic material. Radiological study of the placentas showed gross filling defects to be equally common in the diabetic and non-diabetic placentas. Whether this filling defect is the result of degenerative vascular changes possibly associated with thrombosis, or is due to technical failure to wash out blood clots which formed after separation of the placenta, can only be decided after further combined radiological and histological studies. Until such studies have been made, the possibility should be borne in mind that filling defects may have little or no significance in a full-term placenta when degenerative changes are to be expected, but may be evidence of premature degeneration in the placenta of a 36-week pregnancy.

Our numbers are too small to assess the significance of the association between hyperlipidaemia during

pregnancy and vascular changes in the uterus and placenta, but it is noteworthy that mean levels of β -lipoprotein were lower in patients whose placental histology was normal than in those where it was abnormal, and also in patients whose placentas showed normal vascular filling compared with those showing filling defects. The only two patients with fatty vascular change in the uterine blood vessels had high levels of β -lipoprotein. Further studies are needed to confirm these correlations. At present the possibility cannot be ruled out that hyperlipidaemia may play a part in the causation of premature placental degeneration and thus be a contributory factor to the higher foetal loss in the diabetic pregnancy. Though in our series the five patients with an increased pre- β -lipoprotein fraction from the early months of pregnancy had a successful outcome, Vernet and Smith (1961) found that high concentrations of pre- β -lipoprotein at this stage of pregnancy were commonly associated with foetal loss. Hyperlipidaemia during early pregnancy may be of equal or greater importance in causing placental degeneration than when it occurs later. Randle, Garland, Hales and Newsholme (1963) suggest that in diabetes mellitus a disturbance of lipid metabolism may precede that of carbohydrate metabolism and this hypothesis might explain why the foetal loss is already high during the 'pre-diabetic' phase.

Summary

Serial estimations of serum lipoproteins have been made during pregnancy in 52 diabetic (including 4 'potential diabetic') and 21 non-diabetic women. Between the 12th and 16th weeks of pregnancy the mean levels of total lipid, total cholesterol, phospholipid, and α -lipoprotein lipid were higher in the diabetic group, although the difference was only statistically significant for α -lipoprotein. At this early stage of pregnancy a marked pre- β -lipid band was present in five of the diabetic but in none of the non-diabetic women. After the 16th week all lipid fractions increased steadily and there was no difference between the two groups. After the 32nd week α -lipoprotein decreased in the non-diabetic but remained raised in the diabetic women. No correlation was found between the serum lipoprotein levels and the outcome of the pregnancy.

Serum total lipid, total cholesterol, and phospholipid levels in the cord blood of 31 infants of diabetic mothers were higher than those in infants of non-diabetic mothers. The highest levels were found in infants of diabetic women (including 'potential diabetics') not treated with insulin.

Biopsies from the rectus muscle and uterus from 24 diabetic women were examined by light microscopy:

in 2 of these patients fatty change was present in the uterine blood vessels, and these women had the highest levels of β -lipoprotein. No fatty change was seen in the control material. Placental vasculature was studied by light microscopy and by radiography after the injection of barium. Histological examination showed no distinctive features in the diabetic placentas. Radiological examination showed areas of defective filling in some placentas from both diabetic and non-diabetic women. The maternal serum lipoproteins were higher in the diabetic women whose placentas showed defective filling than in those with normal filling.

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