Type II Hyperlipoproteinemia in Mother and Twins

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SUMMARY
A 36-year-old housewife with type II hyperlipoproteinemia became pregnant with twins. Although the pregnancy was uneventful, the serum triglycerides were elevated during the third trimester, the delivery, and early puerperium. The mother had no complications directly related to the pregnancy despite hypercholesterolemia, coronary atherosclerosis, and hypertension. Cord blood cholesterol and beta lipoprotein in both twins were greater than twice normal. Despite this genetic defect in lipid transport the twins have developed normally during their first year of life. Since lipids and lipoproteins do not cross the placental barrier, it is concluded that type II hyperlipoproteinemia may have been present at birth.

Additional Indexing Words:
Lipid changes with pregnancy  Hyperbetalipoproteinemia  Infants  Cord lipids

Report of Case
A 36-year-old woman with labile hypertension and hypercholesterolemia was hospitalized for observation in January 1966 following several cholesterol measurements of over 500 mg%. Physical examination showed mild obesity, xanthelasma, tendon xanthomata on wrists and ankles, and a bruit over the left carotid artery.

Serum cholesterol levels* were 375 mg% to 570 mg% (normal range: 150 to 280 mg%), phospholipids were 347 mg% (normal range: 205 to 340 mg%), and total serum lipids were 1,074 mg% (normal range: 400 to 1,000 mg%).2

An electrocardiogram showed nonspecific ST-T changes with multiple atrial premature contractions. The double two-step exercise test produced 1 mm horizontal depression of the S-T segment in aVF, V5, and V6 with no chest pain or dyspnea. Lipoprotein electrophoresis studies (fig. 1) showed densely stained beta bands and faint pre-beta bands when serum from the mother and two of her four children was used. This finding was consistent with hyperbetalipoproteinemia. The patient's mother had hypercholesterolemia (387 mg%) and hypertriglyceridemia (386 mg%), and lipoprotein electrophoresis studies showed a prominent beta band and moderate pre-beta band. Other members of the family had cardiovascular disease (fig. 2).

The patient had a 3-year history of labile hypertension and hypercholesterolemia with no complaints of chest pain or dyspnea. Previous pregnancies were normal. She had had tendon xanthomata on both hands at age 19, and xanthelasma at age 30. Her father, who had xanthelasma and angina pectoris, died at age 48 of a myocardial infarction.

In subsequent clinic visits, the patient's serum

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*The method of determination of cholesterol was reported in 1967.1

†The method of Lees and Hatch was used for lipoprotein electrophoresis.3

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ELECTROPHORESIS with DIFFERENTIAL STAINS

PROTEIN
(Bromphenol Blue Stain)

FAT or LIPOPROTEIN
(Oil Red O Stain)

J.N.

Normal

Figure 1

Electrophoretic patterns of mother compared to normal patterns. The top electrophoretic strip is a routine protein stain using a barbital (Veronal) buffer and bromphenol blue stain. The middle and lower strips are buffered and stained specifically for fat using a 1% albumin buffer and oil red O stain. Note that the rate of migration of β-lipoprotein is the same as β-globulin. The middle strip was performed on serum of patient prior to pregnancy. Density of the β-lipoprotein in the middle strip shows marked increase when compared to the normal in the lower strip. The prominent β-lipoprotein band with a faint pre-beta band is consistent with a diagnosis of hyperbeta-lipoproteinemia (Fredrickson type II).

cholesterol level averaged 410 mg%, and her blood pressure ranged from 140/70 to 170/95.

In January 1967 she was diagnosed as 10 weeks pregnant and placed on a low cholesterol diet (erratically followed) with oral iron, multivitamins, mild tranquilizers, and diuretic therapy with potassium supplementation.

She was again admitted to the hospital for evaluation and management at 32 weeks' gestation. At this time the uterus was larger than anticipated, and a fetogram confirmed a twin pregnancy. Blood pressure ranged from 110/70 to 130/84. Blood count, serum electrolytes, and renal function were normal. Serum cholesterol and triglyceride levels* were elevated (fig. 3) and a low fat diet was ordered.

Three weeks before the expected date of delivery labor began spontaneously, showing normal fetal presentations. A pudendal block (1% Carbo-caine) was given.

The patient's blood pressure rose from 130/80 during the first and second stages of labor to 180/112 in the third stage; 30 min following the administration of phenobarbital the blood pressure was 160/110. The electrocardiogram showed no change during labor and delivery, and the patient did not complain of chest pain or dyspnea. Blood pressure gradually returned to 130/90 during the subsequent 24 hours.

The twins were born 8 minutes apart, and the girl presented first. Cholesterol levels were elevated in cord blood samples. Physical examinations showed both twins to be normal. They were

*The method of determination of triglycerides was reported in the Technicon Symposium. 4
The father of the twins was not the father of the mother's previous children. The prevalence of cardiovascular disease on the mother's side of the family tree is striking.

Discussion

Prior to pregnancy the patient's lipids were elevated, the cholesterol levels averaging 412 mg% and the triglycerides, 119 mg%. On two determinations, however, the serum triglycerides were found to be slightly elevated (137 mg% and 157 mg%, respectively). The phospholipids averaged 333 mg%, and the total lipids averaged 1,039 mg%. The serum lipoprotein electrophoretic pattern (fig. 1), which showed an intensely stained beta band with a faint pre-beta band, was consistent with Fredrickson's type II hyperlipoproteinemia.

However, during pregnancy the patient's serum cholesterol level did not increase like that of nonhypercholesterolemic patients during pregnancy. The serum cholesterol level averaged 440 mg% in the first trimester, 436 mg% in the second trimester, and 353 mg% in the third trimester (fig. 3). The serum lipid electrophoretic pattern showed no visible change in the cholesterol-rich beta band during pregnancy (fig. 3). During labor and delivery the serum cholesterol levels fluctuated slightly.

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*Ross Laboratories, Columbus, Ohio.
†Mead-Johnson Co., Evansville, Indiana.
Serum triglyceride levels showed the largest increase during pregnancy, rising from an average of 119 mg% before pregnancy, to 170 mg% in the first trimester and 347 mg% during the third trimester. This is similar to the elevations of serum triglycerides reported for nonhypercholesterolemic patients during pregnancy. On the electrophoretic pattern, the pre-beta band (glyceride-rich fraction) increased steadily during pregnancy, labor, and delivery, then decreased in the puerperium. Serum triglyceride values decreased 100 mg% after delivery of the first infant and rose transiently after delivery of the second. Labor began approximately 7 hours after an evening meal; therefore, triglyceride levels during labor and after the second birth could still be elevated by exogenous triglyceride. Exogenous triglyceride may be seen in figure 3 as chylomicrons at the points of origin on the electrophoretic strips obtained during and immediately after delivery.

Total lipids increased only slightly during pregnancy from an average level of 1,039 mg% in the nonpregnant state to 1,259 mg% in the third trimester. Total serum lipids rose 100

Figure 3

Serum lipoprotein electrophoresis on a fasting specimen during the first trimester of pregnancy was similar to the electrophoretic strip taken before pregnancy in figure 1. During late pregnancy and delivery there was marked increase in stain of the glyceride-rich pre-beta band. By the fourth postpartum day the serum triglyceride and pre-beta band had decreased but were still abnormal. By the fourth postpartum week the beta-lipoprotein band and serum cholesterol had both risen—presumably because of poor adherence to low fat diet. An unexpected finding was the persistent triglyceride elevation (221 mg%) several weeks after delivery.

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HYPERLIPOPROTEINEMIA IN MOTHER AND TWINS

Newborn and Maternal Lipoprotein Electrophoresis

**NEWBORN**

<table>
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<th></th>
<th>α</th>
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<tbody>
<tr>
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<td>43</td>
<td></td>
</tr>
<tr>
<td>Male Twin</td>
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<td>J.N.</td>
</tr>
<tr>
<td>Female Twin</td>
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**MOTHERS**

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*Figure 4*

*Lipid values in mother and newborn infants 10 days after delivery. The normal newborn and mother's electrophoretic strips are shown above the line; below the line are the type II strips from the twins and mother with intensely stained beta-lipoprotein bands.*

mg% during labor and early puerperium as expected.%

The twins' cord serum cholesterol was 151 mg% for the male and 111 mg% for the female, which is approximately two or three times that found in normals. The paper lipid electrophoresis showed a marked increase in the beta band in both infants. Figure 4 shows the difference between the lipoprotein electrophoresis of the twins and a normal infant and their respective mothers. During the first 4 weeks of life, on a normal diet, there were no significant changes in the serum lipids or lipoproteins of the twins or the normal infants.

Pregnancy is not advisable for a patient with hypercholesterolemia and coronary artery disease. However, this patient presented an opportunity to investigate the lipid changes occurring in a patient with type II hyperlipoproteinemia.

Therapy for reduction of serum cholesterol included diet, but hypocholesterolemic agents were not used. Cholestyramine was not used because of its frequent gastrointestinal side effects. Choloxin, the D-isomer of thyroxine, was not used because of its possible elevation of the basal metabolic rate and precipitation of angina pectoris. Clofibrate was not used because of the possibility of impairing maternal and fetal cholesterol synthesis by the liver and theoretically affecting fetal hepatic function.

The fall in serum cholesterol during hospitalization was unexpected, although the patient probably did not observe her diet while at home. However, Green observed that dietary restriction does not prevent the rise of serum cholesterol in normal or hypercholesterolemic pregnant patients. The expected increase of serum triglycerides did occur.

Rafstedt has made a detailed study of lipid and lipoprotein levels in normal newborn infants. Recent studies of lipoprotein levels in normal mothers and infants in the perinatal period confirmed that fetal lipoproteins cannot be correlated with those of the mother. Placental transfer of either lipoproteins or lipids as covered by Auerswald and Dancis confirmed that the lipoproteins in the infant's cord were probably synthesized in utero by the fetus. This is substantiated by our data which show a difference between the lipids and the lipoproteins of the twins as well as differences between maternal and cord lipids. It is possible that small amounts of lipids may cross the placenta, but most fetal lipids and lipoproteins are synthesized in utero.

The cholesterol and lipoprotein values in these two infants were abnormal at birth. Rafstedt gives the range of cord blood beta
lipoprotein as 51 to 158 mg% with a mean of 103 mg%. Auerswald’s\textsuperscript{15} range of cord blood S\textsubscript{f} 0 to 12 lipoproteins by ultra-centrifugation was 78 to 143 mg% with a range of 290 to 554 mg% for the mother at the same time. Normal cord cholesterol, according to Rafstedt, is 48 to 90 mg% with a mean of 75 mg%.

It appears, therefore, that the type II lipid transport disturbance begins in utero. Diet alone did not account for the hypercholesterolemia, since the infants had elevated cholesterol levels before feedings. As Fredrickson and others have emphasized, prophylaxis against atherosclerosis should start early in childhood. Treatment should not be delayed until the second or third decade when the symptoms appear. Our data indicate therapy probably should begin in infancy.

Acknowledgment

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References

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