Pregnancy in a Patient With Homozygous Familial Hypercholesterolemia Undergoing Low-Density Lipoprotein Apheresis by Dextran Sulfate Adsorption

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Pregnancy and delivery in homozygous familial hypercholesterolemic (HFH) patients is extremely rare. We describe the case of a woman with HFH treated with low-density lipoprotein (LDL) apheresis by dextran sulfate adsorption who became pregnant and reached delivery uneventfully. LDL apheresis was performed biweekly, and lipoprotein analyses in pre-apheresis samples showed progressive increases in triglyceride, total cholesterol, LDL cholesterol, and apolipoprotein (apo) B plasma concentrations. The fractional catabolic rate (FCR) for LDL cholesterol, as estimated by the first-order disappearance constants (*k* values) of the recovery of LDL cholesterol concentration to basal values after each apheresis session, increased more than threefold from week-24 to week-4 (labor is considered as time 0). After delivery, basal values were recovered, but normalization was slower for LDL cholesterol than for the other lipidic parameters. High-density lipoprotein (HDL) showed a different pattern: HDL_3 remained stable throughout gestation, whereas HDL_2 cholesterol and apo A-I had a maximum at midgestation, then declined, and finally increased again at late gestation. With the exception of this latter increase of HDL_2, all the other changes in lipoprotein concentrations during pregnancy and postpartum were similar to those found in healthy women. Thus, LDL apheresis does not interfere with physiologic adaptations of lipoprotein metabolism during pregnancy in HFH patients.

FAMILIAL HYPERCHOLESTEROLEMIA is an inherited disorder of lipoprotein metabolism caused by abnormalities in the cell-surface receptor for low-density lipoprotein (LDL).[1] The homozygous state is rare, occurring in one in 1 million individuals, and is characterized by a serum cholesterol level between 600 and 1,000 mg/dL, early appearance of cutaneous and tendinous xanthomas, and onset of coronary artery disease in childhood.[2] Death due to myocardial infarction frequently occurs in homozygotes before they reach the age of 20 years.[3] Patients with homozygous familial hypercholesterolemia (HFH) are notoriously resistant to treatment with diet and drugs. Extracorporeal removal of cholesterol is the only widely available therapy that yields a reproducible benefit in these patients.[4]

Pregnancy and delivery in HFH women is extremely rare.[5] Recently, two cases of uncomplicated term pregnancy in HFH women treated with plasmapheresis have been described.[6,7] No complications from the procedure were apparent in either mother or fetus. LDL apheresis and adsorption with dextran sulfate columns is a more selective and effective treatment for reduction of plasma LDL than plasmapheresis.[8] We describe an uneventful pregnancy in a HFH woman undergoing LDL apheresis with dextran sulfate columns.

CASE REPORT

The patient, a 27-year-old woman, had presented at 7 years of age with cutaneous and tendinous xanthomas on elbows, knees, and Achilles tendon. Her serum cholesterol level was between 800 and 1,000 mg/dL. Her biologic parents had hypercholesterolemia, and in both paternal and maternal families there were numerous cases of hypercholesterolemia and cardiovascular disease. Cutaneous xanthomas were surgically removed. At 17 years of age, she started treatment with plasmapheresis (one session per month with a volume exchange of 2 L per session). Serum cholesterol concentrations oscillated between 600 and 700 and 300 and 350 mg/dL (preplasmapheresis and postplasmapheresis values). At 26 years of age, she was referred to our Hospital for LDL apheresis by dextran sulfate adsorption. LDL receptor deficiency was confirmed by the inability of LDL cholesterol to reverse lymphocyte proliferation during cholesterol synthesis inhibition with lovastatin.[9] An angiographic study showed a mild valvular aortic stenosis with an aortic gradient of 40 mm Hg, without significant coronary lesions.

Brief Description of the Technique

The dextran sulfate is negatively charged and adsorbs the positively charged apolipoprotein (apo) B lipoproteins, mainly LDL. When the column containing dextran sulfate is saturated with LDL, it may be regenerated by 4.1% NaCl, which completely restores its binding capacity.

We use the Kaneka MA 01 monitor (Kaneka, Osaka, Japan) with a plasma separator (Sulflux FS-05; Kanegafuchi Chemical Industry, Osaka, Japan) and two dextran sulfate columns (Liposorber LA-15; Kagenafuchi Chemical Industry). The patient's blood is continuously withdrawn from an antecubital arteriovenous fistula and anticoagulated with a bolus of heparin 0.8 mg/kg. Blood flux is maintained between 125 and 150 mL/min. Plasma flow rate is set at 35% the flow rate of blood. The plasma is separated with a plasma filter and then passed through one of the dextran sulfate columns, which retains the apo B–containing lipoproteins. After filtering 500 mL plasma, the monitor automatically switches to the second dextran sulfate column, while the first one is regenerated. Apo B lipoprotein–free plasma is recombined with the blood cells and reinfused to the patient. The dead volume of the system is approximately 400 mL. The duration of a session is 3 hours, and 8,000 mL plasma is treated.

LDL apheresis by dextran sulfate adsorption is an effective and selective method for extracorporeal LDL cholesterol removal. LDL can be decreased to 15% of the initial value in a single session by treating three times the plasma volume of the patient.[10] In contrast, high-density lipoprotein (HDL) and other serum proteins including albumin, immunoglobulins, and antithrombin III do not

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adsorb to dextran sulfate, and consequently their plasma concentrations remain unchanged.[8] To study the efficacy of LDL apheresis in the present case, two blood samples were withdrawn every session, one before (pre-apheresis) and one just after cessation of LDL apheresis (post-apheresis). Total cholesterol and triglyceride levels were measured in plasma by enzymatic-colorimetric methods (Menarini Diagnostici, Florence, Italy). Total HDL and HDL_3 cholesterol levels were measured after separation from plasma by sequential precipitation with dextran sulfate/$MgCl_2$,[11] and HDL_2 cholesterol level was calculated by difference. LDL cholesterol level was estimated by the Friedewald formula.[12] Apo B and apo A-I levels were measured by nephelometric methods (Beckman Instruments, Palo Alto, CA) with World Health Organization standards.

To study the dynamics of lipoprotein changes after each LDL apheresis, the first-order disappearance constants (k values) were calculated according to the method reported by Apstein et al,[13] by considering the initial steady-state concentration before the first LDL apheresis (783 mg/dL), the minimum concentration after each apheresis session (post-apheresis values), the concentration at the beginning of the following apheresis session (pre-apheresis values), and the time (in days) elapsed between consecutive treatments. This way, obtained k values are equivalent to fractional catabolic rates (FCRs).[13,14]

RESULTS

Upon entering this clinic, the patient was kept on a low-cholesterol diet without drug treatment and subjected to LDL apheresis by dextran sulfate adsorption, initially with a periodicity of one session per week for 6 months. The mean pre- and post-apheresis concentration during this treatment period were, respectively, 331 ± 29 and 85 ± 9 mg/dL for total cholesterol and 271 ± 27 and 36 ± 9 for LDL cholesterol. The clinical evolution and other biochemical data have been previously reported.[10] After 6 months of treatment, the subject became pregnant; apheresis was interrupted for 2 months and then reinitiated with a periodicity of every other week until 1 month before labor, when it was interrupted again. No complications from the procedure were apparent in either maternal or fetal heart rates. Pregnancy proceeded uneventfully, and fetal growth was determined to be normal by ultrasonography. At the 39th week of gestation, the patient had a vaginal delivery of a female infant weighing 2,900 g. Histopathologic examination of the placenta and umbilical arteries showed no atherosclerotic changes, infarctions, or lipid deposits. Total cholesterol level in the umbilical cord was 68 mg/dL. At 11 months of age, the child had a total cholesterol level of 175 mg/dL, LDL cholesterol of 137, and apo B of 125. Two months after labor, total cholesterol concentration in the mother reached 1,086 mg/dL, and LDL apheresis was reinitiated, being regularly performed every other week up to the present time.

Plasma lipid and apolipoprotein values during gestation, postpartum, and postlactation periods are listed in Tables 1 and 2. Both the pre-apheresis and post-apheresis values are shown, and only periods with regular LDL apheresis every 2 weeks are considered. Concentrations of total cholesterol, LDL cholesterol, and apo B in pre-apheresis samples increased progressively during gestation; values 8 weeks before labor were almost two times greater than values 24 weeks before labor (Table 1). After labor, and once LDL apheresis was reinitiated, lipid values greatly decreased, but total cholesterol and LDL cholesterol still were significantly higher than in the control period. Triglyceride concentration increased to an even greater extent than cholesterol during gestation, from 75 to 242 mg/dL, and returned to basal values in postpartum (Table 1).

The efficiency of the apheretic procedure, calculated as the extent of total cholesterol removal as a percentage of the pre-apheresis values, varied during gestation: it was 67.2% ± 0.8% in the third trimester (weeks −14 to −6), as compared with 73.8% ± 0.2% in the second trimester

Table 1. Pre- and Post-Apheresis Plasma Concentrations of Total Cholesterol, Total Triglyceride, LDL Cholesterol, and Apo B During Gestation, Postpartum, and Postlactation in a HFH Patient Treated With Dextran Sulfate LDL Apheresis Every 2 Weeks

Period	Total Cholesterol		Total Triglyceride		LDL Cholesterol		Apo B	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Gestation (week)								
−24	449	115	75	19	393	67	328	55
−22	478	131	100	69	415	77	350	69
−20	545	141	108	52	477	85	381	72
−18	563	147	115	70	497	85	400	75
−16	555	147	104	49	486	99	493	92
−14	551	185	148	70	485	133	452	127
−12	618	188	129	67	555	140	486	128
−10	626	188	111	61	570	145	518	136
−8	717	242	242	117	627	177	582	159
−6	704	250	273	129	606	182	564	169
−4	809	—	242	—	712	—	678	—
Postpartum (weeks 12-26)	540 ± 10	127 ± 3	75 ± 6	43 ± 8	484 ± 9*	81 ± 3	369 ± 8	64 ± 3
Postlactation (weeks 28-56)	495 ± 9	118 ± 2	73 ± 4	34 ± 3	441 ± 8	77 ± 2	382 ± 9	64 ± 2

NOTE. Values correspond to samples drawn immediately before (pre) or after (post) each apheresis session. Values of gestation are shown individually for every session (from weeks −24 to −4; labor is considered time 0). Those corresponding to postpartum (weeks 12-26 after labor) and postlactation (weeks 28-56 after labor) are the mean ± SEM (n = 7 and n = 15, respectively). Statistical comparisons between postpartum and postlactation were made by Neuman-Keuls multiple-range analysis.

*$P < .01$.

Table 2. Pre- and Post-Apheresis Plasma Concentrations of HDL, HDL_3, and HDL_2 Cholesterol, and Apo A-I During Gestation, Postpartum, and Postlactation in a HFH Patient Treated With Dextran Sulfate LDL Apheresis Every 2 Weeks

Period	HDL Cholesterol		HDL_3 Cholesterol		HDL_2 Cholesterol		Apo A-I	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Gestation (week)								
−24	41	43	28	29	13	14	118	117
−22	43	40	28	25	14	15	121	119
−20	47	45	29	28	18	17	121	123
−18	43	44	32	33	12	11	121	114
−16	49	47	35	34	14	13	119	112
−14	37	38	33	30	4	8	105	110
−12	37	35	28	26	9	9	108	101
−10	33	30	30	28	3	3	115	103
−8	42	42	39	39	3	3	113	116
−6	44	42	32	30	11	12	112	118
−4	49	—	31	—	18	—	135	—
Postpartum (weeks 12-26)	40 ± 2	38 ± 1	28 ± 1	22 ± 3	13 ± 1	13 ± 1	103 ± 4	104 ± 2
Postlactation (weeks 28-56)	39 ± 1	35 ± 2	29 ± 1	25 ± 2	10 ± 1	11 ± 1	102 ± 2	102 ± 2

NOTE. Values and protocol are as in Table 1. No significant differences were found ($P > .05$).

(weeks −24 to −16, $P < .001$), 76.3% ± 0.6% in postpartum ($P < .001$), and 76.2% ± 0.6% in postlactation ($P < .001$). Reasons for the lower relative efficiency of the apheretic procedure are the higher initial cholesterol concentration in late gestation and the plasma volume treated, which was constant in all the sessions (8 L), whereas the patient's total plasma volume increased during gestation. When the decrement of plasma total cholesterol concentration in each LDL apheresis session was calculated, a more pronounced effect was observed in the third than in the second trimester of gestation (433 ± 18 *v* 381 ± 17 mg/dL plasma, respectively, $P < .05$), which is attributed to the different pre-apheresis plasma cholesterol concentrations.[15]

HDL lipid and apo A-I values are listed in Table 2. The apheretic procedure produced a slight decrease in plasma total HDL cholesterol concentration, which corresponded to a decrease in only the HDL_3 subfraction. Apo A-I was not retained in the dextran sulfate columns, since plasma concentrations in post-apheresis samples were almost identical to those found in pre-apheresis samples (Table 2). HDL cholesterol and apo A-I concentrations, as well as HDL-subfraction distribution, in postpartum were similar to those found in postlactation (control period) and in the first part of gestation examined (weeks −24 to −16). Thereafter in gestation, both apo A-I and HDL cholesterol decreased, a change that affected only HDL_2. This low concentration of HDL_2 cholesterol lasted for at least 6 weeks (weeks −14 to −8). In the last period of gestation, both HDL_2 cholesterol and apo A-I progressively increased, reaching values at week −4 that were even higher than at midgestation and postpartum. In contrast, HDL_3 cholesterol concentration remained stable during gestation and postpartum as compared with postlactation.

To estimate the LDL cholesterol FCR, we calculated the *k* values according to the method reported by Apstein et al.[13] LDL cholesterol FCR increased progressively during gestation greater than threefold (Table 3). In postpartum, FCR declined but still was significantly higher than in postlactation, where it was 0.051 pools per day, a value similar to the one obtained in this patient in a pregestational period (0.049 ± 0.005 pools per day).[10]

DISCUSSION

HFH is a rare lipid disorder resistant to conventional lipid-lowering therapy. The prognosis of the condition is extremely poor. Patients usually die by myocardial infarction in their teens. Consequently, pregnancy in HFH women is exceptional. Plasma exchange has improved the prognosis of HFH patients. Nowadays, there is agreement that extracorporeal cholesterol-removal procedures are the elective treatment for these patients, since a significant increase in the life span can be expected.[4]

Table 3. LDL Cholesterol *k* Values in Response to LDL Apheresis During Gestation, Postpartum, and Postlactation in a HFH Patient Treated With Dextran Sulfate LDL Apheresis Every 2 Weeks

Period	k(pools · d^{-1})
Gestation (week)	
−26 to −24	0.0388
−24 to −22	0.0555
−22 to −20	0.0596
−20 to −18	0.0636
−18 to −16	0.0610
−16 to −14	0.0591
−14 to −12	0.0748
−12 to −10	0.0789
−10 to −8	0.1003
−8 to −6	0.0879
−6 to −4	0.1521
Postpartum (weeks 12-26)	0.0586 ± 0.0030*
Postlactation (weeks 28-56)	0.0510 ± 0.0016

NOTE. Values of gestation are shown individually for the 2-week intervals between sessions (weeks −26 to −4; labor is considered time 0). Those corresponding to postpartum (weeks 12-26 after labor) and postlactation (weeks 28-56 after labor) are the mean ± SEM (n = 7 and n = 15, respectively). Statistical comparisons between postpartum and postlactation were made by Neuman-Keuls multiple-range analysis.

*$P < .05$.

Pregnancy in HFH women treated with extracorporeal techniques is more feasible. Two cases of pregnancy in women treated with plasmapheresis have been described.[6,7] LDL apheresis with dextran sulfate columns is a more selective and efficient procedure for extracorporeal cholesterol removal than plasmapheresis.

The hyperlipidemic effect of gestation is well known.[16,17] In normal women, there are progressive increases in very–low-density lipoprotein (VLDL) and LDL during gestation, with the change being more important for triglyceride than for cholesterol.[16,18] In our patient, progressive increases in pre-apheresis values of total cholesterol, LDL cholesterol, apo B, and total triglycerides were also observed during gestation. Similar changes in LDL were reported in pregnant patients with familial hypercholesterolemia.[5,19,20] Therefore, these increases in pre-apheresis values observed in our patient reflect the hyperlipidemic effect of gestation.

To gain better insight into the dynamics of the hyperlipidemia of pregnancy, k values of the recovery of plasma LDL cholesterol concentration after each apheresis session were calculated.[13] As demonstrated by Apstein et al,[13] the k values obtained are estimates of FCRs, and these values also agree closely with fractional production rates obtained by kinetic studies with stable isotopes.[14] We have observed in this HFH patient that in addition to plasma LDL cholesterol in pre-apheresis samples, LDL cholesterol FCR increased progressively during gestation. Similar results were obtained for apo B (data not shown), all of which indicates the augmented production of LDL in this condition. Estimation of absolute LDL cholesterol production rates is not feasible, because steady states were not reached in the different periods and estimates of total plasma volume are not accurate in late gestation; however, by simply comparing the calculated FCRs, it may be anticipated that LDL cholesterol production in late gestation was at least three times greater than in nongestation conditions in this patient. To our knowledge, this is the first time LDL cholesterol production in human gestation has been estimated. An augmented VLDL production rate has been observed by others in the pregnant rat,[21,22] and this is probably also the case in gestating women, in view of the increase of triglyceride plasma levels demonstrated here and in other studies.[16,17] The molecular basis of the augmented VLDL production during gestation is not known, but probably is the result of estrogen action because these hormones stimulate hepatic apo B mRNA transcription[23] and hepatic hydroxymethyl glutaryl coenzyme A reductase activity.[24] In summary, the stimulated VLDL production may account for the augmented LDL cholesterol and apo B production observed during pregnancy in this patient with LDL-receptor deficiency.

HDL cholesterol concentration follows a contrasting biphasic pattern during gestation in normal women, whereby a maximum increase is seen by 20 weeks of gestation and then there is a gradual decline by the end of this period.[16,17] We have observed a similar pattern in our HFH patient, with maximum HDL cholesterol and apo A-I concentrations by midgestation. This increase corresponded to the HDL_2 subfraction, whereas HDL_3 remained stable throughout the study period. Similar results on HDL-subfraction distribution have been observed by others in normal women.[25] Interestingly, after this zenith of HDL_2 and apo A-I at midgestation, we observed a decline from week -14 to week -8. A high HDL_2 plasma concentration has been also observed by others at 35 to 36 weeks of gestation in normal women, which has been linked with the increase in estrogen levels.[26] With regard to the decline in HDL_2 levels from week -14 to -8 in this patient, other causes may apply, including the increase in cholesteryl ester transfer activity[27] and their use for steroid hormone synthesis. In this respect, it has been demonstrated that HDL_2 is an alternative source of cholesterol for progesterone synthesis by human trophoblast cells.[28] In this HFH patient, the restricted LDL uptake by the placenta may favor the utilization of HDL_2 cholesterol for that purpose, leading to the important reduction in HDL_2 plasma levels in weeks -14 to -8, when progesterone secretion peaks.[29]

In conclusion, we report the changes in lipoprotein concentrations during pregnancy and postpartum in a HFH woman being treated biweekly with LDL apheresis. The lipid profile showed changes similar to those found in healthy women, including increases in triglyceride, LDL cholesterol, and apo B levels as a consequence of increased production rates, as well as the fluctuations of HDL_2 and apo A-I. Therefore, LDL apheresis does not interfere with the physiologic adaptations of lipoprotein metabolism during pregnancy in HFH patients.

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