Atherosclerosis 254 (2016) 179–183

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Lipoprotein apheresis is essential for managing pregnancies in patients with homozygous familial hypercholesterolemia: Seven case series and discussion

Masatsune Ogura [a, *], Hisashi Makino [b], Chizuko Kamiya [c], Jun Yoshimatsu [c], Handrean Soran [d], Ruth Eatough [d], Giuseppina Perrone [e], Mariko Harada-Shiba [a], Claudia Stefanutti [f]

[a] Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan
[b] Division of Endocrinology and Metabolism, National Cerebral and Cardiovascular Center Hospital, Osaka, Japan
[c] Department of Perinatology, National Cerebral and Cardiovascular Center Hospital, Osaka, Japan
[d] Department of Medicine, Central Manchester University Hospital NHS Foundation Trust, Manchester, United Kingdom
[e] Department of Obstetrics and Gynecology, "Sapienza" University of Rome, Roma, Italy
[f] Departments of Immunohematology and Transfusion Medicine and Department of Molecular Medicine – Lipid Clinic and Atherosclerosis Prevention Centre, "Sapienza" University of Rome, Roma, Italy

ARTICLE INFO

Article history:
Received 20 July 2016
Received in revised form
6 October 2016
Accepted 7 October 2016
Available online 8 October 2016

Keywords:
Lipoprotein apheresis
Homozygous familial hypercholesterolemia
Pregnancy
Coronary artery disease
Aortic valvular disease

ABSTRACT

Background and aims: For patients with homozygous familial hypercholesterolemia (HoFH), atherogenic lipoprotein changes and increased stress on cardiovascular system during pregnancy may pose substantial risk for both the mother and her fetus. Although lipoprotein apheresis (LA) is reported as the most effective therapy to control LDL-C levels during pregnancy in HoFH patients, only case reports have been published, and there is no guidance for management.
Methods: We report twelve pregnancies and ten deliveries in seven patients with HoFH, and compare the clinical outcomes between patients who received LA during pregnancy and those who did not.
Results: One patient who refused LA during pregnancy died from acute myocardial infarction after delivery. Another patient whose adherence to LA was poor also died of myocardial infarction during pregnancy. One patient who initiated LA at the age of 18 had to discontinue LA due to severe symptoms of angina pectoris during pregnancy. Another had symptoms of nausea, hypotension, and bradycardia with increased levels of serum bradykinin during a dextran sulfate cellulose absorption-based LA procedure. Although two of the other three patients had already had coronary artery disease by the time of pregnancy, early initiation of LA from childhood and good adherence to it during pregnancy resulted in the delivery of healthy infants without adverse effects.
Conclusions: LA is essential for managing pregnancy safely in patients with HoFH. Increasing numbers of documented cases, including ours, will be helpful to guide future therapeutic decisions.

1. Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare inherited disorder of lipid metabolism with a prevalence of 1:160,000–1,000,000. It is characterized by extremely high levels of low-density lipoprotein cholesterol (LDL-C) since birth. Multiple cutaneous and tendon xanthoma and coronary artery disease (CAD) are evident even in childhood [1].

HoFH patients are usually identified in early childhood because of the appearance of xanthoma associated with an extraordinarily high plasma LDL-C levels. Early initiation of sustained cholesterol-lowering treatment including lipoprotein apheresis (LA), high dose statins, and ezetimibe have reportedly improved longevity in HoFH [2] [3].

Managing these patents during child-bearing age presents many challenges for clinicians because LDL-C increases during gestation,

* Corresponding author. Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan.
E-mail address: enustasam@ncvc.go.jp (M. Ogura).

http://dx.doi.org/10.1016/j.atherosclerosis.2016.10.018
0021-9150/

statins and ezetimibe are contraindicated during pregnancy and lactation, and some patients may have aortic-valve disease and CAD. Therefore, LA is regarded as the most effective therapy to control LDL-C levels during pregnancy in patients with HoFH [4] [5] [6] [7]. However, only a few cases of pregnancy in HoFH patients have been reported and there is no guidance for overall management. In addition, costs, availability, vascular access, patient's commitment and willingness to accept LA pose practical challenges to provide LA for more patients.

In this paper, we describe 12 pregnancies and 10 deliveries in 7 HoFH women treated with or without LA during pregnancy.

2. Patients and methods

The clinical features of our cases are based on retrospective data from medical files.

3. Results

The clinical characteristics of the patients are described in Table 1. The details of LA procedures before and during pregnancy and lactation in each patient are described in Table 2.

3.1. Patient 1

The patient was diagnosed with HoFH when she was 9 years old based on having tendon xanthoma and high concentration of total cholesterol (TC) ≥700 mg/dL. Biweekly plasma exchange (PEX) was initiated at the age of 11 years. However, adherence to PEX was poor and was discontinued by the patient at 17 years old. An electrocardiogram exercise test at the age of 18 years was abnormal with ST depression in the inferio-lateral leads. Additionally, carotid and subclavian bruits were detected. Subsequently, PEX was restarted but interrupted for many months due to a holiday abroad. Coronary angiography showed severe ostial stenosis in the right coronary artery as well as in the left circumflex coronary artery resulting in the patient undergoing a coronary artery bypass graft (CABG) at the age of 19 years. Three years later, magnetic resonance imaging showed extensive arterial disease and a redo of the CABG was performed. The patient received pre-conceptional advice along with genetic counseling. A year later, and back on biweekly PEX, she became pregnant and discontinued atorvastatin as contraindicated in pregnancy. The progression of the pregnancy caused the patient to experience increased chest tightness and dyspnea. The frequency of LA was increased to weekly in mid-second trimester. The birth was an uneventful, vaginal delivery. Liver transplantation was considered after the first delivery and discussed with the patient, but she embarked on her second pregnancy before a decision had been made. The patient declined liver transplantation and recommenced lipid-lowering therapy. The patient's symptoms matched the first pregnancy with increased chest tightness and dyspnea. During this pregnancy the patient attended for PEX on a regular basis and went on to have a normal vaginal delivery. The patient died of a sudden myocardial infarction at the age of 31 years. Her family reported that the coroner's inquest had shown that she was approximately 20 weeks pregnant with her third pregnancy. Her family also reported she had discontinued medication and PEX during the last few months of her life.

3.2. Patient 2

The patient was clinically diagnosed with HoFH at the age of 10 years based on high level of serum TC (791 mg/dL) and the presence of multiple xanthoma. She had a LDL-receptor gene mutation (Exon 14-P664L) and both parents were heterozygous FH (HeFH). At 23 years of age, coronary angiography showed no significant atherosclerotic lesion; however, aortography showed aortic valvular calcification and ascending aorta dilatation. By the age of 23 years, she underwent weekly LA by double filtration plasmapheresis (DFPP) and lipid-lowering drug therapy (statins and cholestyramine). She announced an unplanned pregnancy at the age of 25 years and had her last session of LA, she refused to attend for LA during her pregnancy for fear of its consequences. She delivered a female baby weighing 3000 g by Caesarean section (CS). CS was indicated by arrest of dilatation. The baby was breast-fed for eight months. The patient recommenced LA at 15-day intervals as she refused to be treated on weekly basis. Angiography of aorta and coronary arteries was performed at the age of 27 years, which showed significant stenosis in the left circumflex artery. There was also severe stenosis of the aortic valve associated with supravalvular aortic stenosis. She had surgical replacement of the aortic valve and ascending aorta with the pulmonary autograft with reimplantation of the coronary arteries and pulmonary outflow reconstruction. The patient was also diagnosed with a pulmonary embolism. On her discharge, LA was increased to weekly. Two months later, she died of acute myocardial infarction.

3.3. Patient 3

The patient was clinically diagnosed with HoFH at the age of 7

Table 1
Clinical characteristics of patients with homozygous familial hypercholesterolemia.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age diagnosed (years)	9	10	7	3	1	4	3
Age LA initiated (years)	11	10	18	22	4	12	9
Mutation details	Unknown	*LDLR* homo c.2054C > T. p.P685L	Unknown	*LDLR* homo c.2054C > T. p.P685L	*LDLR* homo 1845 + 2 T > C	Unknown	*LDLR* compound hetero c.667_680 dup c.2416_2417 ins
CAD prior to first pregnancy (years)	CABG (19 and 22)	No	CABG [18and19]	CABG (22)	No	No	Total occlusion of RCA (25)
AVD prior to first pregnancy (years)	No	ascending aorta dilatation (23)	No	No	No	No	Supra-aortic valvular stenosis (25)
LLT before pregnancy	Atorvastatin cholestyramine	Atorvastatin cholestyramine	Probucol	Atorvastatin probucol	Atorvastatin probucol	Cholestyramine atorvastatin	Atorvastatin
LLT after pregnancy	Atorvastatin ezetimibe	Atorvastatin cholestyramine	probucol	Rosuvastatin probucol	Atorvastatin probucol	Atorvastatin ezetimibe	Atorvastatin ezetimibe
Patients' outcome	Died of AMI at 31 years of age	Died of AMI at 27 years of age	Alive	Alive	Alive	Alive	Alive

LA, lipoprotein apheresis; LDLR, low-density lipoprotein receptor; CAD, coronary heart disease; CABG, coronary artery bypass graft; RCA, right coronary artery; AVD, aortic valvular disease; LLT, lipid lowering treatment; AMI, acute myocardial infarction.