

Successful Direct Adsorption of Lipoproteins (DALI) Apheresis During Pregnancy in an Omani Woman with Homozygous Familial Hypercholesterolemia

Tamima Al-Dughaiishi¹, Khalid Al-Waili², Yajnavalka Banerjee³, Shahila Sheik¹, Hilal Al-Sabti⁴, Ibrahim Al-Zakwani^{5,6}, Suad Al-Mukhaini⁷, Khalifa Al Wahaibi⁸, Ali T. Al-Hinai⁹ and Khalid Al-Rasadi^{2,*}

¹Department of Obstetrics & Gynecology, Sultan Qaboos University Hospital, Muscat, Oman

²Department of Clinical Biochemistry, Sultan Qaboos University Hospital, Muscat, Oman

³Department of Biochemistry, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman

⁴Department of Surgery, Cardiothoracic Unit, Sultan Qaboos University Hospital, Muscat, Oman

⁵Department of Pharmacology and Clinical Pharmacy, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman

⁶Gulf Health Research, Muscat, Oman

⁷Department of Nursing, Sultan Qaboos University Hospital, Muscat, Oman

⁸Department of Surgery, Vascular Unit, Sultan Qaboos University Hospital, Muscat, Oman

⁹Ministry of Health, Muscat, Oman

Abstract: We report our experience with Direct Adsorption of Lipoproteins (DALI) apheresis in an Omani pregnant woman affected by homozygous familial hypercholesterolemia. To the best of our knowledge this is the first successful pregnancy treated with DALI apheresis.

The patient had a history of coronary artery disease, supra-aortic valvular stenosis and severe carotid artery disease with right carotid artery stenting. She was on a regular biweekly DALI apheresis since 2008. In May 2013, she became pregnant and rosuvastatin and ezetimibe were stopped while she continued on DALI apheresis biweekly. This treatment during pregnancy was successful with no major complications. The average low-density lipoprotein cholesterol reduction during therapy was 50%. She spontaneously delivered a healthy male infant (2,400 g) at 37 weeks. We showed that DALI apheresis therapy was safe during pregnancy with a good outcome for both mother and neonate.

Keywords: Familial hypercholesterolemia, low density lipoprotein receptor, xanthoma, LDL-apheresis, pregnancy.

INTRODUCTION

Homozygous Familial Hypercholesterolemia (HoFH) is an inherited disease caused by genetic defects in low-density lipoprotein receptors (LDLRs), apolipoprotein B (Apo B) and proprotein convertase subtilisin/kexin type 9 (PCSK9) [1, 2] HoFH is characterized by very high levels of low-density lipoprotein cholesterol (LDL-C) and if not recognized and treated early it will lead to severe cardiovascular disease (CVD) early in life [3-5] HoFH is treated by combination of statin with or without ezetimibe and regular LDL apheresis [6-15].

High concentrations of LDL-C levels during pregnancy may have serious consequences for both the fetus and mother. It may increase the risk of acute myocardial ischemia for women who have underlying coronary artery disease (CAD) [6-19] and it may cause fetal intrauterine growth restriction [20-22]. The use of statins is contraindicated during pregnancy and LDL apheresis should be considered in the management of pregnant women with HoFH.

There are several reported cases of successful pregnancy with FH treated with plasma exchange [23, 24], heparin extracorporeal LDL-C precipitation (HELP) [25, 26], or dextran sulphate-cellulose adsorption (DSA) [27, 28], cascade filtration system [29] and immunoabsorption (IA) [30] apheresis. For direct adsorption of lipoproteins (DALI) apheresis, there was one reported case of apheresis therapy

*Address correspondence to this author at the Department of Clinical Biochemistry, Sultan Qaboos University Hospital, PO Box 38, Al-Khodh, PC-123, Sultanate of Oman, Tel: +968-96780908; Fax: +968-24141786; E-mail: khalid77@squ.edu.om

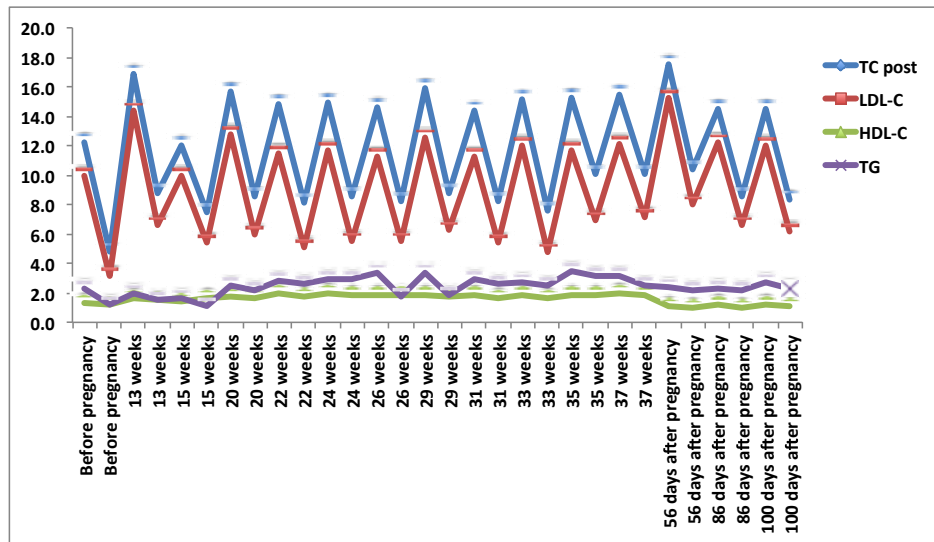


Fig. (1). Lipid levels pre and post LDL-apheresis before, during and after pregnancy.

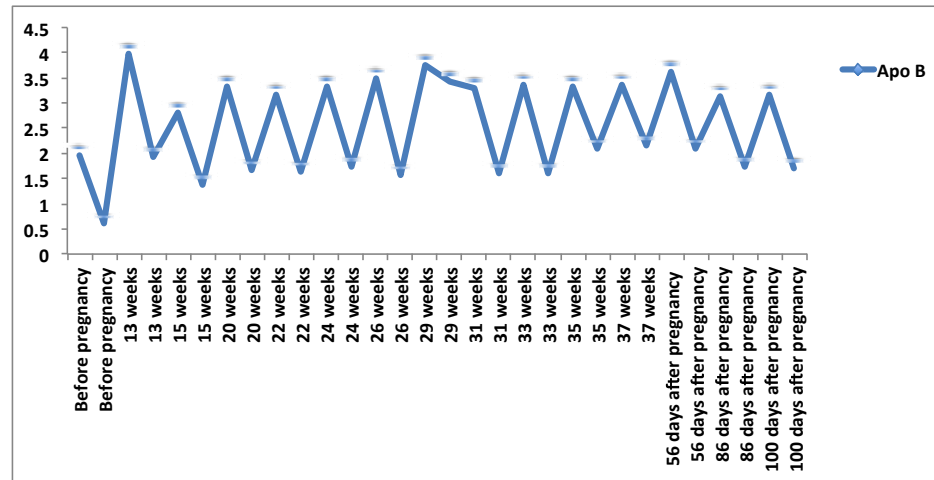


Fig. (2). Apo B levels pre and post LDL-apheresis before, during and after pregnancy.

during pregnancy but the treatment was not successful and was stopped at 28 weeks because of severe tetany related to treatment [31]. To our knowledge, we report the first successful pregnancy involving a HoFH patient treated with DALI apheresis **Fig. (1) and Fig. (2)**.

CASE REPORT

The patient was a 38-year old woman diagnosed with HoFH with LDL-receptor mutation at exon 4 G397A and PCSK9 mutation at exon 9 A1420G. She was on rosuvastatin 40 mg and ezetimibe 10 mg. In addition, she was on biweekly DALI LDL-apheresis using a left arm basilic arterio-venous (A-V) shunt. She had carotid artery disease with a right carotid endarterectomy in 2004 and right carotid stent. She had moderate supravalvular aortic stenosis on echocardiogram but with normal left ventricular function and evidence of CAD on angiography in 2006 with minimal left

anterior descending disease. The patient remained asymptomatic through the years and responded very well to pharmacological treatment and LDL-apheresis.

Prior to this pregnancy, she had 2 live children in good health but had lost 3 pregnancies. When she became pregnant this time, rosuvastatin and ezetimibe were discontinued while she was continued on low fat diet. Her pregnancy was managed by a multidisciplinary team consisting of obstetric, cardiology and lipid specialists. Due to her high risk background and LDL-C of 14.4 mmol/L, she was continued on LDL-apheresis. All the biweekly DALI were performed with the DALI 750 adsorbers (Fresenius HemoCare Adsorber Technology GmbH, St. Wendel, Germany). In each session, an average of 7,100 ml of whole blood was processed in about 2 h, at an average rate of 60 ml/h. Anticoagulation in the extracorporeal system was carried out by acid citrate dextrose (ACD-A) infusion and was first mixed with the patient’s blood at a ratio of 1:20 and

Table 1. Baseline lipid profile for the family.

	TC mmol/L	LDL-C mmol/L	HDL-C mmol/L	TG mmol/L	Apo B g/L	Apo A1 g/L
Husband	6.0	3.8	1.08	2.3	1.19	1.38
Wife (patient)	16.9	14.4	1.67	2.0	3.97	1.79
Daughter 1	7.4	5.6	0.98	1.8	1.52	1.19
Daughter 2	7.7	5.6	1.24	1.7	1.52	1.41
Daughter 3	6.7	5.0	1.38	0.9	1.26	1.33
Son 1	8.4	6.1	1.10	2.8	1.69	1.18
Son 2 (New born)	4.1	1.9	0.73	3.3	0.87	1.19

reduced to 1:40 after 1,500 ml of blood was treated. Average calcium levels were 2.43 mmol/L and the patient was receiving oral calcium supplements before each apheresis therapy. Fetal monitoring was performed before and after DALI apheresis and no fetal heart rate abnormalities were detected. The first DALI-apheresis resulted in a 54% reduction of LDL-C levels to 6.6 mmol/L (Table 1).

The patient continued to receive DALI-apheresis until 37 weeks of gestation with average blood pressure (BP) 132/54 mmHg, blood glucose 5.1 mmol/L, glycosylated hemoglobin (HbA_{1c}) 6.2%, weight 82 Kg and body mass index (BMI) 36. She had uncomplicated spontaneous vaginal delivery of a healthy boy weighing 2,400 g. From Week 13 to 37 of her pregnancy, the patient received 12 DALI-apheresis to control cholesterol levels.

DISCUSSION

Pregnancy in women with HoFH carries risk to the mother and fetus. High maternal cholesterol may cause growth restriction, preeclampsia and miscarriage in animal and human studies [32, 33]. Pregnancy in women with HoFH is contraindicated and there are no clear guidelines for their management. Nevertheless, there are several reported cases in the literature of women treated with apheresis using plasma exchange, HELP, DSA, cascade filtration system and IA apheresis [23-30].

This is the first case of successful pregnancy outcome using the DALI apheresis system. A previous report with DALI apheresis was not successful and the apheresis was stopped at 28 weeks of gestation due to severe tetany but the pregnancy was carried out to term [31]. In our case and prior to the current pregnancy and the commencement of DALI apheresis, the woman had 2 healthy babies and 3 miscarriages. She was diagnosed with severe carotid artery disease, moderate supra-avalvular aortic stenosis and mild CAD. Although, she was counseled against undertaking pregnancy the decision after she became pregnant was to provide appropriate management of her cholesterol levels and the risk prevent further worsening of her cardiovascular disease.

The most suitable anticoagulants for apheresis during pregnancy are unfractionated low molecular weight heparin and citrate. Low molecular weight heparin has fewer side effects, is well tolerated and does not pass the blood-brain

barrier [34]. In addition, apheresis or plasma exchange with citrate was also used in pregnant women [35, 36]. In our case the use of ACD-A infusion as anticoagulant was proved to be safe with very minimal side effects of paresthesia around the mouth and the jaw during the sessions and this did not result in discontinuation of treatment.

In our lipid and LDL apheresis unit at Sultan Qaboos University hospital in Oman we have identified 5 HoFH with molecular genetic confirmation and we have reported previously 2 of these cases including the current reported case [37-39]. We had lost one of the HoFH who was a female child with very severe HoFH and severe atherosclerosis. Currently four HoFH, one heterozygous FH (HeFH) with severe CAD and one HeFH with statin intolerance and CAD are receiving regular DALI apheresis in our unit.

In conclusion, this is the first case report of a successful pregnancy outcome in a patient with HoFH treated with DALI apheresis. In general, although pregnancy and delivery in women with HoFH and cardiovascular disease are hazardous and should be monitored very closely, long-term LDL apheresis seems feasible to control superimposed hyperlipidemia, cardiovascular disease, placental insufficiency and subsequent intrauterine growth restriction.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaud AL, Sly WS, Valle D, Eds. *The metabolic and molecular bases of inherited disease*. 8th ed. New York, NY: McGraw-Hill; 2001: pp. 2863-2913.
- [2] Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am J Epidemiol* 2004; 160: 407-420.
- [3] Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis* 2003; 168: 1-14.

- [4] Austin MA, Hutter CM, Zimern RL. Familial hypercholesterolemia and coronary heart disease: a HuGE association review. *Am J Epidemiol* 2004; 160: 421-429.
- [5] Yuan G, Wang J, Hegele RA. Heterozygous familial hypercholesterolemia: an underrecognized cause of early cardiovascular disease. *CMAJ* 2006; 174: 1124-1129.
- [6] Raal FJ, Pilcher GJ, Panz VR. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. *Circulation* 2011; 124: 2202-2207.
- [7] Kolovou GD, Dedoussis GV, Anagnostopoulou KK, *et al.* Management of a patient with a null low-density lipoprotein receptor mutation: a case report. *Angiology* 2006; 57: 729-732.
- [8] Gagne C, Gaudet D, Bruckert E, Ezetimibe Study Group. Efficacy and safety of ezetimibe co administered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002; 105: 2469-2475.
- [9] Gagne C, Bruckert E, *et al.* Ezetimibe significantly reduces low-density lipoprotein cholesterol in homozygous familial hypercholesterolemia. *J Am Coll Cardiol* 2002; 29: 135B.
- [10] Geiss HC, Otto C, Hund-Wissner E, Parhofer KG. Effects of ezetimibe on plasma lipoproteins in severely hypercholesterolemic patients treated with regular LDL-apheresis and statins. *Atherosclerosis* 2005; 180: 107-112.
- [11] Yamamoto A, Harada-Shiba M, Endo M, *et al.* The effect of ezetimibe on serum lipids and lipoproteins in patients with homozygous familial hypercholesterolemia undergoing LDL-apheresis therapy. *Atherosclerosis* 2006; 186: 126-31.
- [12] Bruckert E, Gagne C, Gaudet D, *et al.* Homozygous familial hypercholesterolemia: a novel therapy with ezetimibe. *Atherosclerosis* 2002; 3: 81.
- [13] Nishimura S, Sekiguchi M, Kano T, *et al.* Effects of intensive lipid lowering by low-density lipoprotein apheresis on regression of coronary atherosclerosis in patients with familial hypercholesterolemia: Japan Low-density Lipoprotein Apheresis Coronary Atherosclerosis Prospective Study (L-CAPS). *Atherosclerosis* 1999; 144: 409-417.
- [14] Tatami R, Inoue N, Itoh H, *et al.* Regression of coronary atherosclerosis by combined LDL-apheresis and lipid-lowering drug therapy in patients with familial hypercholesterolemia: a multicenter study. The LARS Investigators. *Atherosclerosis* 1992; 95: 1-13.
- [15] Thompson GR, Miller JP, Breslow JL. Improved survival of patient 5 with homozygous familial hypercholesterolemia treated by plasma exchange. *Br Med J (Clin Res Ed.)* 1985; 291: 1671-3.
- [16] Aalders K, Huisman A, Bosker HA. Myocardial infarct in the puerperium. *Ned Tijdschr Geneesk* 1998; 142: 1103-5.
- [17] Hameed AB, Padmini P, Goodwin TM. Unstable angina during pregnancy in two patients with premature coronary atherosclerosis and aortic stenosis in association with familial hypercholesterolemia. *Am J Obstet Gynecol* 2000; 182: 1152-5.
- [18] Glaser D, Hubert R, Beythien RD, Schuster H, Pawlowitzki H. Fatal re-infarct in pregnancy. *Geburtshilfe Frauenheilkd* 1988; 48: 656-8.
- [19] Wallenburg HCS: Maternal haemodynamics in pregnancy. *Fet Med Rev* 1990; 2: 45-66.
- [20] Barss V, Phillippe M, Greene MF, Covell L. Pregnancy complicated by homozygous hypercholesterolemia. *Obstet Gynecol* 1985; 65: 756-7.
- [21] Beigel Y, Hod M, Fuchs J, *et al.* Pregnancy in a homozygous familial hypercholesterolemic patient treated with long-term plasma exchange. *Am J Obstet Gynecol* 1990; 162: 77-8.
- [22] Palinski W, Napoli C. The fetal origins of atherosclerosis: maternal Hypercholesterolemia, and cholesterol-lowering or antioxidant treatment during pregnancy influence in utero programming and postnatal susceptibility to atherogenesis. *FASEB J* 2002; 16: 1348-60.
- [23] Beigel Y, Bar J, Cohen M, Hod M. Pregnancy outcome in familial homozygous hypercholesterolemic females treated with long-term plasma exchange. *Acta Obstet Gynecol Scand* 1998; 77: 603-8.
- [24] Goldstein BL, Hofshire PJ, Sears TD, *et al.* Long-term plasmapheresis in the homozygous hyperlipemic patient. *Am Heart J* 1991; 122: 1465-6.
- [25] Cashin-Hemphill L, Noone M, Abbott JF, Waksmonski CA, Les RS. low-density lipoprotein apheresis therapy during pregnancy. *Am J Cardiol* 2000; 86: 1160, A10.
- [26] Anedda S, Mura S, Marcello C, Pintus P. HELP LDL-apheresis in two cases of familial hypercholesterolemic pregnant women. *Transfus Apher Sci* 2011; 44: 21-4.
- [27] Kroon AA, Swinkels DW, van Dongen PWJ, Stalenhoif AF. Pregnancy in a patient with homozygous familial hypercholesterolemia treated with long-term low-density lipoprotein apheresis. *Metabolism* 1994; 43: 1164-70.
- [28] Mora C, Teruel JL, Navarro JF. Low-density lipoprotein apheresis in homozygous familial hypercholesterolemia. *Am J Cardiol* 2001; 88: 202-3.
- [29] Erterer ME, Guvenc B, Haydardedeoglu B, Tekinturhan F. A case report of the cascade filtration system: a safe and effective method for low-density lipoprotein apheresis during pregnancy. *Ther Apher Dial* 2008; 12: 396-400.
- [30] Blaha M, Lanska M, Boudys L, *et al.* Pregnancy in homozygous familial hypercholesterolemia- a successful case. *Abstracts/Nutrition* 2013; 29:1434-6.
- [31] Sblinger JL, Brignon P, Grunenberger I. Traitement par LDL-apherese au cours de la grossesse. *Presse Med* 2003; 32: 1031-2.
- [32] DeAssis SM, Seguro AC, Helou CM. Effects of maternal hypercholesterolemia on pregnancy and development of offspring. *Pediatr Nephrol* 2003; 18: 328-34.
- [33] Thadhani R, Stampfer MJ, Hunter DJ, Manson JE, Solomon CG, Curhan GC. High body mass index and hypercholesterolemia: risk of hypertensive disorders of pregnancy. *Obstet Gynecol* 1999; 94: 543-50.
- [34] Heilmann L, Rath W, Friedrich von Tempelhoff G, *et al.* Niedermolekulare heparine in der schwangerschaft. *Dt. Arzteblatt* 2002; 99/7: C320-C5.
- [35] Dittrich E, Schmaldienst S, Langer M, Jansen M, Horl WH, Derfler K. Immunoabsorption and plasma exchange in pregnancy. *Kidney Blood Press Res* 2002; 25: 232-9.
- [36] Swoboda K, Derfler K, Koppensteiner R, *et al.* Extracorporeal lipid elimination for treatment of gestational hyperlipidemic pancreatitis. *Gastroenterology* 1993; 104: 1527-31.
- [37] Al-Hinai AT, Al-Abri A, Al-Dhuhli H. First case report of familial hypercholesterolemia in an Omani family due to novel mutation in the low-density lipoprotein receptor gene. *Angiology* 2013; 64: 287-92.
- [38] Al-Rasadi K, Al-Waili K, Al-Zidi WA. Low-density lipoprotein receptor gene mutation analysis and structure-function correlation in an Omani Arab family with familial hypercholesterolemia. *Angiology* 2014; 65: 911-8.
- [39] Al-Waili K, Al-Zidi WA, Al-Abri AR. Mutation in the PCSK9 gene in Omani Arab subjects with autosomal dominant hypercholesterolemia and its effect on PCSK9 protein structure. *Oman Med J* 2013; 28: 48-52.