

Safe Continuation of Apheresis during Pregnancy using the Double-Filtration Plasmapheresis Thermo Mode in a Pregnant Female with Familial Hypercholesterolemia: A Case Report

Yoshimasa Sakurabu¹, Haruhito A. Uchida¹, Yuka Okuyama¹, Eriko Eto², Kanako Takasugi¹, Tomohiko Asakawa¹, Katsuyoshi Katayama¹, Shugo Okamoto¹, Yasuhiro Onishi¹, Natsumi Matsuoka-Uchiyama¹, Chihiro Fujihara³, Keiko Tanaka¹, Hidemi Takeuchi¹, Ryoko Umebayashi¹, Katsuyuki Tanabe¹ and Jun Wada¹

¹Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Faculty of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

²Department of Obstetrics and Gynecology, Okayama University Hospital, Okayama, Japan

³Department of Clinical Engineering Center, Okayama University Hospital, Okayama, Japan

Familial hypercholesterolemia (FH) is an inherited disorder characterized by elevated LDL cholesterol levels and an increased risk of early-onset atherosclerotic cardiovascular disease. In pregnant female with FH, apheresis is the preferred treatment because standard therapeutic agents such as statins are contraindicated during pregnancy. LDL adsorption therapy is commonly used; however, after 27 weeks of gestation, it is often switched to dual filtration plasma exchange (DFPP) due to the significant drop in blood pressure caused by bradykinin production. However, DFPP has limited ability to adapt to the increase in circulating plasma volume associated with pregnancy. Here we discuss the case of a 32-year-old female with homozygous FH who underwent different apheresis strategies during her pregnancies. In her first pregnancy, she continued LDL adsorption therapy using DFPP but ultimately delivered a small-for-gestational-age infant via cesarean section. For her second pregnancy, double-filtration plasmapheresis thermo mode, DF-thermo, was introduced to mitigate the limitations of DFPP and LDL adsorption therapies, such as hypotension during apheresis and albumin loss. By minimizing these complications, DF-thermo allowed for a successful delivery without compromising fetal growth.

Key words: Familial hypercholesterolemia, Double-filtration plasmapheresis thermo-mode, Pregnancy

Introduction:

Familial hypercholesterolemia (FH) is a genetic disease characterized by elevated low-density lipoprotein (LDL) cholesterol concentration and early onset of atherosclerotic cardiovascular disease. Treatment of FH includes a low-fat diet and smoking cessation guidance and management of comorbidities such as diabetes and hypertension, use of statins and other medications and LDL apheresis¹. Although most therapeutic agents such as statins are contraindicated in pregnant females with FH, with a

few exceptions, continued apheresis during pregnancy is desirable to ensure appropriate lipid management for increased cardiovascular stress due to increased blood coagulation capacity, platelet function, and blood viscosity during pregnancy². Here we discuss a case in which double-filtration plasma exchange therapy (DF-thermo) was successfully applied to a pregnant patient with FH, allowing for effective LDL cholesterol management within the target range while minimizing hypotension and albumin loss.

Address for correspondence: Haruhito A. Uchida, Department of Chronic Kidney Disease and Cardiovascular Disease, Okayama University Faculty of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama, 700-8558, Japan. E-mail: hauchida@okayama-u.ac.jp

Received: March 10, 2025 Accepted for publication: July 6, 2025

Copyright©2026 Japan Atherosclerosis Society

This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

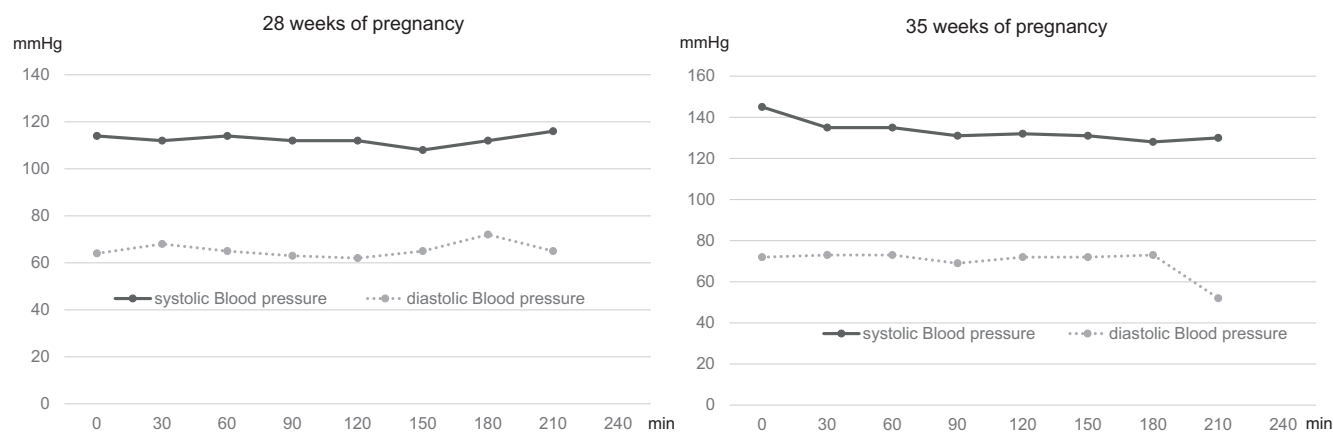


Fig. 1. Blood pressure changes during plasma exchange

The graph on the left shows the blood pressure trend during plasma exchange immediately after admission to our hospital. The graph on the right shows the blood pressure trend during plasma exchange just before delivery. Both demonstrate no obvious drop in blood pressure during plasma exchange.

Case:

A 32-year-old female with homozygous FH (HoFH) became pregnant with her second child and was referred to our department and the obstetrics and gynecology department for continued apheresis treatment and delivery management five months before her expected delivery date. The patient was diagnosed with HoFH at the age of 2 years with cutaneous xanthomas, xanthomas tendinosum and elevated LDL cholesterol (LDL-C) concentration above 1000 mg/dL; however, the details of her genetic testing are not known. The patient began LDL apheresis therapy at the age of 7 years and continued statin treatment until the age of 14. Subsequently, the patient was switched to LDL apheresis therapy alone, and her blood test data at that time were TC 249mg/dL and LDL-C 194mg/dL, having delivered her first child three years ago at another hospital. A cesarean section was performed at 37 weeks of gestation. The fetus weighed 1,992 g and was diagnosed with mild preeclampsia.

On her first physical examination, the patient was 27 weeks pregnant, and her weight had dropped to 53.4kg due to hyperemesis gravidarum. Her blood pressure was 130/66 mmHg, pulse 70/min (regular rhythm), respiratory rate was 18 breaths/min, and O₂ saturation was 97% on room air. She did not have any abnormal findings, such as xanthomas, in patients with FH. Echocardiography revealed no cardiac dysfunction, left ventricular hypertrophy, or abnormal left ventricular wall motion. Her lipid profile showed a total cholesterol (T-Cho) concentration of 450 mg/dL, triglyceride (TG) of 348 mg/dL, a low-density

lipoprotein cholesterol (LDL-C) level of 346 mg/dL, and HDL of 54 mg/dL. Her albumin level was low (2.9 g/dL). Other data, including thyroid function, liver function and creatinine kinase levels, were within the normal ranges. Ultrasonographic examination of the carotid arteries revealed no significant atherosclerotic changes. She had a history of switching from LDL apheresis to DFPP at birth; however, during treatment, she experienced a strong sense of nasal obstruction, ocular conjunctival hyperemia and fatigue. In addition, while on DFPP, she was unable to aggressively increase her plasma processing volume due to a drop in her albumin level; DF-thermo was selected because it was easier to increase the processing volume. DF-thermo used Plasmaflow® OP-08D as the primary membrane and Cascadeflo® EC-50W as the secondary membrane. Apheresis via a vascular access catheter in the jugular vein was performed at blood flow rates between 100 and 140 mL/min. Between 27 and 36 weeks of gestation, her blood pressure remained stable during the DF-thermo. After the transition to DF-thermo, she experienced a significant improvement in the sensation of nasal obstruction, conjunctival hyperemia, fatigue, and resolved nasal obstruction compared with LDL apheresis performed before admission (**Fig. 1**). Although the guidelines do not provide clear criteria for pregnant female with FH, the goal for FH without a history of coronary artery disease is usually an LDL-C concentration of <100 mg/dL; therefore, we set the treatment goal accordingly. At approximately 31 weeks of gestation, her post-treatment LDL concentration began to increase. We incrementally increased the plasma processing volume during apheresis to account for the

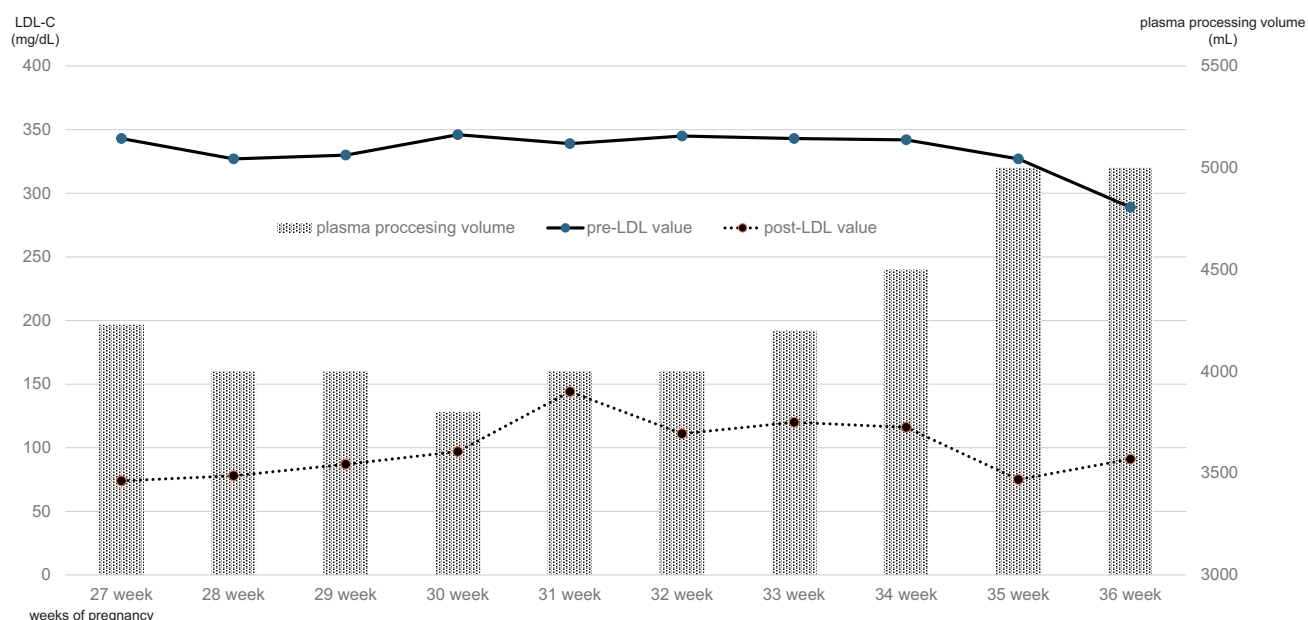


Fig. 2. LDL cholesterol concentration and the amount of plasma processing volume in plasma exchange

Beginning at 31 weeks' gestation, post-plasma exchange LDL cholesterol concentrations rose and exceeded management goals. After a stepwise increase in plasma processing volume, the post-plasma exchange LDL cholesterol concentration showed improvement. After 35 weeks of gestation, the LDL cholesterol concentration was kept within the target.

increase in circulating plasma volume associated with pregnancy. When the plasma processing volume was increased to 5.0 L, the post-treatment LDL-C level was maintained within the target values (Fig. 2). The pre-treatment albumin concentration remained between 2.8 and 3.1 g/dL and temporarily decreased to 2.4-2.6 g/dL immediately after treatment but recovered at the next apheresis (Fig. 3). The fetus grew well during treatment with DF-thermo (Fig. 4). At 36 weeks of gestation, she was diagnosed with hypertensive disorders of pregnancy due to an elevated blood pressure of 158/80 mmHg, a urine protein/creatinine ratio of 1.53 g/gCr and bi-lateral lower leg edema. The patient was deemed to require emergency hospitalization for maternal management, consequently, she went into labor the same night that she was admitted. She underwent an emergency cesarean section the next morning and gave birth to a 2,492g baby at 36 weeks and 1 d of gestation. The neonate's Apgar score was 8/9, and her clinical progress was good with no postoperative hemostasis. DF-thermo was repeated in the first week after delivery, and the patient was discharged.

Discussion:

FH is an autosomal hereditary disease with three main features: hyperlipidemia, early coronary artery disease and tendon and skin xanthomas³. Patients

with FH have a rapid progression of atherosclerotic lesions due to their innate high LDL cholesterolemia and hence have a significantly higher prevalence of coronary artery disease and peripheral arterial disease than non-FH patients⁴. However, it is important, though, to prevent the development and progression of atherosclerotic cardiovascular disease through early detection and the prompt initiation of appropriate treatments after diagnosis⁵. In addition to treating patients with FH using statins alone or in combination with ezetimibe, a PCSK9 inhibitor, or other drugs, apheresis may be considered for adjunctive LDL cholesterol reduction in critically ill patients who are unable to achieve target LDL cholesterol levels with pharmacotherapy or other treatment modalities⁶. In contrast, drug therapies other than bile acid sequestrants, such as cholestyramine and omega-3 fatty acids, are not recommended for pregnant female with FH because of the risk of teratogenicity^{7, 8}. For primary prevention, the target LDL-C concentration is set at <100 mg/dL; however, no definitive target has been established for pregnant females with FH. Pregnant females with FH also have elevated LDL-C and TG levels during the second trimester of pregnancy⁹. Hypercholesterolemia causes vascular endothelial damage by decreasing NO production and inducing a vasoconstrictive response, which may cause fetal growth retardation due to decreased uteroplacental

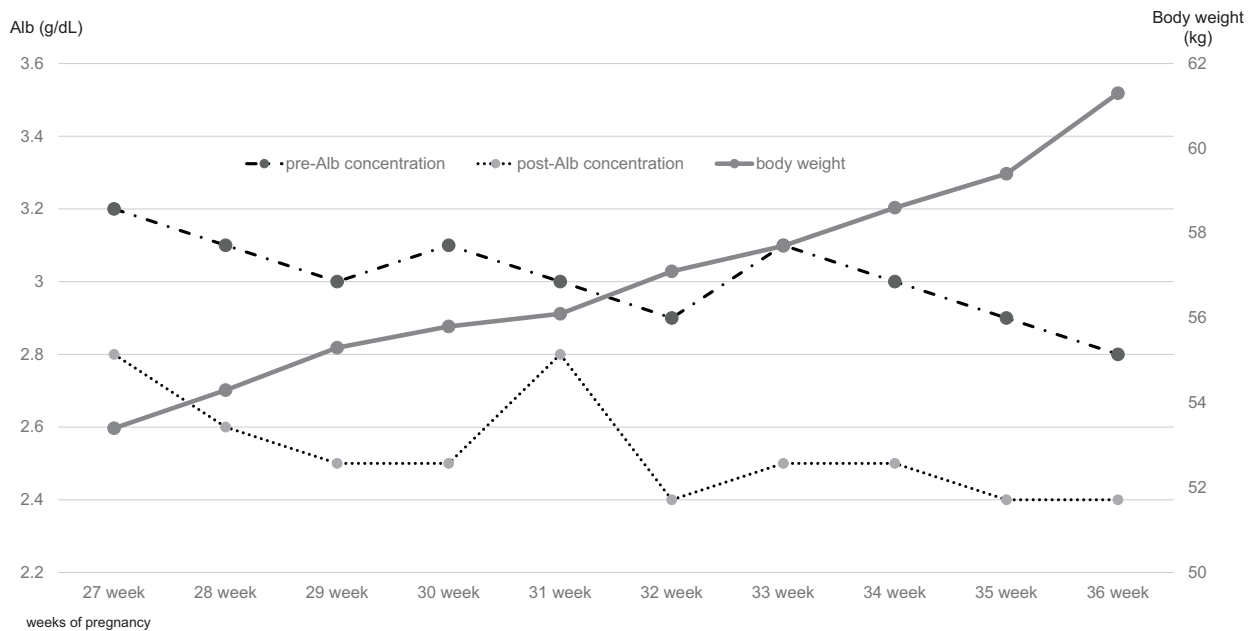


Fig. 3. Maternal weight changes and serum albumin concentration before and after plasma exchange

After plasma exchange, serum albumin concentration decreased to less than 3.0 g/dL, but before plasma exchange the following week, serum albumin concentration improved to approximately 3.0 g/dL or more. This result indicates that albumin loss associated with plasma exchange was limited, and maternal weight increased steadily with each successive gestational week.

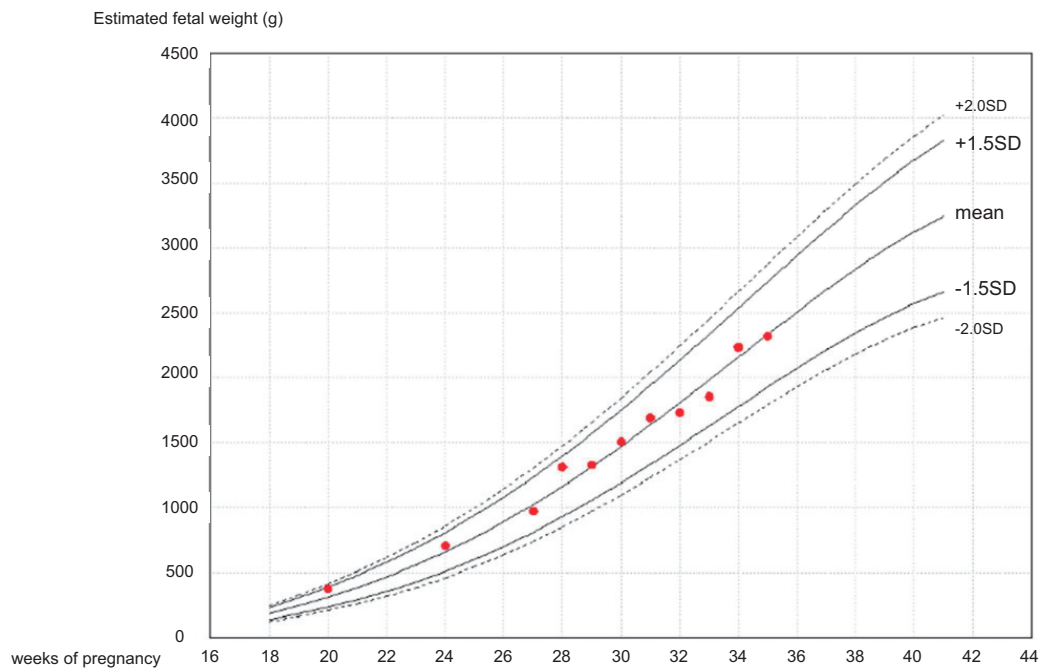


Fig. 4. Estimated fetal weight

Estimated fetal weight (red circle) increased steadily and remained within ± 1.5 SD.

blood¹⁰). Appropriate lipid management is necessary to reduce maternal cardiovascular risk and ensure a safe delivery, however, controlling cholesterol

concentrations is challenging due to limited pharmacological therapy, as described above. Therefore, patients are encouraged to continue stable

Table 1. Comparison of each apheresis modality

Modality		
LDL-Absorption (*1)	Features	• After separating the blood cell and plasma components, the positively charged LDL cholesterol in the plasma component is removed by adsorption onto a cellulose gel on which negatively charged dextran sulphate is fixed, returning it to the body.
	Advantages	• Less adsorption of albumin and other useful proteins, so supplementation with albumin etc. is in principle unnecessary. • The volume per adsorber is small and can cope with small extracorporeal circulating volumes.
	Disadvantages	• Contraindicated in patients taking ACEi.
DFPP (*2)	Features	• After separation of the plasma, etiological agents are removed using a separation membrane. • Lost albumin is replenished.
	Advantages	• Compared to simple plasma exchange, the removal rate of HDL cholesterol is lower and VLDL and LDL cholesterol are selectively removed.
	Disadvantages	• Limited plasma throughput due to the fact that albumin and globulin are also removed by the secondary membrane, and due to clogging of the secondary membrane and consequent increase in membrane pressure.
DF-thermo (*3, 4, 5)	Features	• Use of large-bore membranes with high albumin permeability in plasma fractionators.
	Advantages	• No displacement fluid required • Increased plasma throughput and improved fractional separation performance are observed. • Recirculation system for waste plasma ensures that no plasma effluent is generated externally and infection control is effective.
	Disadvantages	• Plasma throughput increases in a temperature-dependent manner, but improved permeability properties are only seen up to 42°C, with Fib precipitating out due to thermal denaturation when heated above 45°C.

Abbreviation ACEi; angiotensin-converting-enzyme inhibitor, LDL; low density lipoprotein, HDL; high density lipoprotein, VLDL; very low-density lipoprotein, DFPP; Double filtration plasmapheresis

*1 Kobayashi S. Applications of LDL-apheresis in nephrology. Clin Exp Nephrol. 2008; 12: 9-15.

*2 Hirano R, Namazuda K, Hirata N. Double filtration plasmapheresis: Review of current clinical applications. Ther Apher Dial. 2021; 25: 145-151.

*3 Eguchi K, Hirayama C, Yokoi R, Kaneko I, Mineshima M, Akiba T. Japanese Journal of Apheresis. 2005; 24: 39-46.

*4 Eguchi K, Minematsu Y, Kaneko I, Moriyama T, Kawashima A, Mineshima M, Akiba T. Japanese Journal of Apheresis. 2005; 24: 84-90.

*5 Minematsu Y, Eguchi K, Konno Y, Kaneko I, Mineshima M, Akiba T. Japanese Journal of Apheresis. 2006; 25: 145-152.

apheresis treatment throughout pregnancy. However, after 27 weeks of gestation, LDL adsorption therapy is often associated with a significant decrease in blood pressure, likely due to bradykinin production. Accordingly, several patients require a switch to double-filtration plasma exchange (DFPP)^{11, 12}. Compared with simple plasma exchange, DFPP selectively removes LDL-C and very low-density lipoprotein (VLDL). However, DFPP has been noted to have limitations in terms of increasing the volume of processed plasma as the circulating plasma volume expands during pregnancy. This is due to the removal of albumin and globulin by the secondary membrane, as well as the increased membrane pressure caused by secondary membrane clogging¹³.

In our case, we used the DF-thermo mode, in which a heater was inserted into the recirculation circuit and plasma components were heated to a constant temperature for separation operations, thus preventing an increase in plasma viscosity caused by a decrease in plasma temperature and increasing plasma

processing volume and fractionation separation performance¹⁴ (**Fig. 5**). In DF-thermo, the Evaflux-5A (Clara Medical) was used as the plasma separator, whereas the Evaflux-4A was used as the plasma separator in previous LDL apheresis therapies. With Evaflux-4A, an albumin loss of 15-20 g was an issue for a plasma processing volume of 3000 mL, and in many cases albumin replacement was required (**Table 1**). Furthermore, DF-thermo uses a large-pore membrane with high albumin permeability for the plasma component fractionator, which separates relatively small fractions such as albumin, HDL and IgG from large fractions such as LDL, IgM, fibrinogen and TG, allowing small molecules such as albumin to be returned to the body. Blood preparations were no longer required as a replacement fluid. This increases the recovery of albumin levels and reduces the risk of infection¹⁵.

Our patient was treated for LDL adsorption during pregnancy with her first child and experienced adverse events during treatment, including congestion

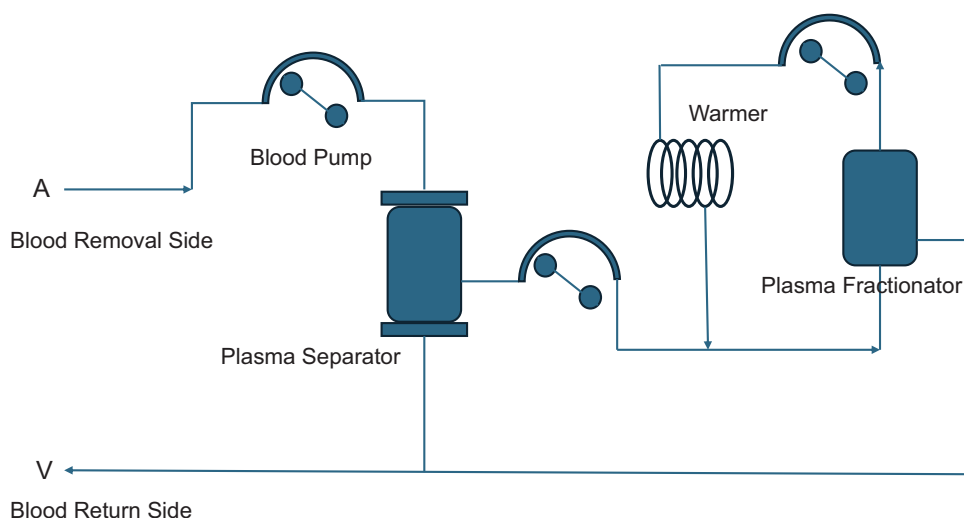


Fig. 5. Circuit Diagram of DF-thermo

Plasma components separated by the plasma separator are heated. After heating, the plasma components are passed through the plasma fractionator for fractionation and separation, resulting in increased plasma throughput and improved fractionation and separation performance.

of both eyes, nasal congestion and hypotension. The LDL adsorption therapy was eventually changed to DFPP, and the above adverse events were alleviated; however, at 37 weeks of gestation, the patient began to have irregular uterine contractions and abdominal pain during apheresis, and prolonged deceleration appeared during fetal heart rate monitoring, resulting in an emergency cesarean section. For the poor post-treatment lowering of LDL concentrations from around 31 weeks of gestation, the plasma processing volume was gradually increased from 33 weeks of gestation, and the volume was finally increased to 5.0 L with no interruption of apheresis due to a drop in blood pressure. Finally, the patient's LDL concentration was maintained within the target level. She was treated for LDL adsorption from non-pregnancy to 26 weeks of gestation. Before starting treatment at our hospital, she experienced worsening post-treatment fatigue in addition to nasal congestion and conjunctival hyperemia. We consider that the negative charge of the adsorption column used in the LDL adsorption activates the blood coagulation system, causing bradykinin to rise, and that bradykinin-mediated hypotension becomes more pronounced from approximately 27 weeks of gestation¹⁶⁾. After transitioning to the DF-thermo method at our hospital, she experienced a reduced sense of nasal obstruction, the conjunctival hyperemia disappeared, and there was no obvious drop in blood pressure, resulting in a stable circulatory dynamic. She also experienced a significant improvement in the subjective symptoms of malaise and fatigue, and safe

perinatal management of mother and fetus. Post-treatment albumin loss was observed; however, improvement was observed before the next treatment, and DF-thermo minimized albumin loss to a limited extent. Thus, the physical condition of pregnant females significantly improved with the use of DF-thermo compared with DFPP. In addition, uterine fetal growth retardation due to maternal nutritional disorders was avoided and the estimated fetal weight increased in line with the standard fetal growth curve, resulting in safe delivery. Altogether, DF-thermo can be an effective treatment for pregnant female with FH, as it benefits both the mother and the fetus.

In conclusion, the clinical usefulness of DF-thermo is suggested for pregnant patients with FH; however, there are still few reports on treatment with this method. Further case studies are needed to realize safer apheresis therapy and delivery management for both pregnant females with FH and the fetus simultaneously, without interfering with the fetal development.

Acknowledgement

We would like to thank Dr. Shiba Mariko of Osaka Medical and Pharmaceutical University for all her kind help. We would like to thank EDITAGE for English language editing.

References

- 1) Varghese MJ. Familial hypercholesterolemia: A review.

- Ann Pediatr Cardiol, 2014; 7: 107-117
- 2) Amundsen AL, Khoury J, Sandset PM, Seljeflot I, Ose L, Tonstad S, Henriksen T, Retterstøl K, Iversen PO. Altered hemostatic balance and endothelial activation in pregnant women with familial hypercholesterolemia. *Thromb Res*, 2007; 120: 21-27
 - 3) EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet*, 2021; 398: 1713-1725
 - 4) Hutter CM, Austin MA, Humphries SE. Familial hypercholesterolemia, peripheral arterial disease, and stroke: a HuGE minireview. *Am J Epidemiol*, 2004; 160: 430-435
 - 5) Harada-Shiba M, Sugisawa T, Makino H, Abe M, Tsushima M, Yoshimasa Y, Yamashita T, Miyamoto Y, Yamamoto A, Tomoike H, Yokoyama S. Impact of statin treatment on the clinical fate of heterozygous familial hypercholesterolemia. *J Atheroscler Thromb*, 2010; 17: 667-674
 - 6) Raal FJ, Pilcher GJ, Panz VR, van Deventer HE, Brice BC, Blom DJ, Marais AD. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. *Circulation*, 2011; 124: 2202-2207
 - 7) Lewek J, Bielecka-Dąbrowa A, Toth PP, Banach M. Dyslipidaemia management in pregnant patients: a 2024 update. *Eur Heart J Open*, 2024; 4: oeae032
 - 8) Al-Baldawi Z, Brown L, Ruel I, Baass A, Bergeron J, Cermakova L, Couture P, Gaudet D, Francis GA, Hegele RA, Iatan I, Mancini GBJ, McCrindle BW, Ransom T, Sherman MH, McPherson R, Genest J, Brunham LR. Sex differences in the presentation, treatment and outcomes of patients with homozygous familial hypercholesterolemia. *J Clin Lipidol*, 2024;18: e189-e196
 - 9) Amundsen AL, Khoury J, Iversen PO, Bergei C, Ose L, Tonstad S, Retterstøl K. Marked changes in plasma lipids and lipoproteins during pregnancy in women with familial hypercholesterolemia. *Atherosclerosis*, 2006; 189: 451-457
 - 10) 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: 603-608
 - 11) Ertorer 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
 - 12) Ogura M, Makino H, Kamiya C, Yoshimatsu J, Soran H, Eatough R, Perrone G, Harada-Shiba M, Stefanutti C. Lipoprotein apheresis is essential for managing pregnancies in patients with homozygous familial hypercholesterolemia: Seven case series and discussion. *Atherosclerosis*, 2016; 254: 179-183
 - 13) Harada-Shiba M, Arai H, Ohmura H, Okazaki H, Sugiyama D, Tada H, Dobashi K, Matsuki K, Minamino T, Yamashita S, Yokote K. Guidelines for the Diagnosis and Treatment of Adult Familial Hypercholesterolemia 2022. *J Atheroscler Thromb*, 2023; 30: 558-586
 - 14) Nakashima M, Yasui M, Ihara A. Fibrinogen salvage during DF Thermo using Evaflux-5A plasma fractionators. *Ther Apher Dial*, 2012; 16: 472-477
 - 15) Hayashi H., Takemura M., Hashimoto H. The experience of double-filtration plasmapheresis thermo-mode (DF thermo) for hemodialysis patients with severe ASO. *Nihon Toseki Igakkai Zasshi*, 2007; 40: 89-94
 - 16) Koga N, Nagano T, Sato T, Kagasawa K. Anaphylactoid reactions and bradykinin generation in patients treated with LDL-apheresis and an ACE inhibitor. *ASAIO J*, 1993; 39: M288-M291