

CASE REPORT

Exposure to alirocumab during the first trimester of pregnancy: A case report

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Abstract

Background: Familial hypercholesterolemia can be efficiently treated with combined lipid-lowering drugs. Lipid-lowering drugs are usually withdrawn for pregnancy and breastfeeding, ideally preconception, followed by lipid apheresis, however, careful plans can be precipitated due to unexpected pregnancy.

Case: A 28-year old woman with familial hypercholesterolemia due to heterozygous *LDLR* mutations had an LDL-cholesterol level at 14.6 mmol/L and Lp(a) at 1150 mg/L. She required a three-vessel coronary artery bypass graft, drug-eluting stents, rosuvastatin, ezetimibe, and alirocumab at maximal dosage. Contraception was advised during the following 12 months, with a planned drug withdrawal to bridge with lipid apheresis, such as the direct adsorption of lipoproteins (DALI). However, an unplanned pregnancy required an abrupt stop of all oral medications at six gestational weeks, except for aspirin. Lipid apheresis controlled LDL-cholesterol in the range of 4.9–7.9 mmol/L (before DALI session) to 1.2–3.2 mmol/L (after DALI session). Later, the regular pregnancy ultrasounds highlighted an isolated agenesis of the corpus callosum later confirmed by magnetic resonance imaging.

Conclusions: A causal link between the early pregnancy exposure to PCSK9 inhibitors (or statins and ezetimibe taken concomitantly) and the observed complete agenesis of the corpus callosum seems unlikely in this case. Guidelines do not specifically recommend preconception measures to lower fetal and/or maternal risks of patients with severe FH considering pregnancy. We argue that lipid apheresis and other measures should be discussed with women with FH and maternity project on an individual basis, until pharmacoepidemiology studies assessing the safety of PCSK9 inhibitors in pregnancy are available.

KEYWORDS

corpus callosum agenesis, familial hypercholesterolemia, PCSK9 inhibitors, pregnancy

Sébastien Kissling and Tinh-Hai Collet contributed equally to this manuscript.

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1 | INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant disease causing elevated low-density lipoprotein cholesterol levels (LDLc) and cardiovascular diseases at early age (Mach et al., 2020). Clinical guidelines recommend combined treatment to lower LDLc with intensive lifestyle programs, high-intensity statin, and ezetimibe. When the target LDLc level cannot be achieved, monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) are the next therapeutic option (Mach et al., 2020; Thompson et al., 2017). This novel drug class can be used in all adults, including young women of childbearing age, although reproductive safety data are missing. In rare situations, extracorporeal clearance of lipoproteins with lipid apheresis is required to control LDLc in FH, especially when the aforementioned therapies are not tolerated or contraindicated (France et al., 2016; Mach et al., 2020; Watts et al., 2015). Here, we report the clinical case of a woman with FH who became pregnant while on statin, ezetimibe, and a PCSK9 inhibitor.

2 | CASE REPORT

At medical check-up, a 28-year-old Caucasian woman reported exertion dyspnea. She was otherwise healthy and sedentary, but reported second-hand smoking at home. Her father had had a hemiparetic stroke at 50 and a fatal heart infarct at 52 years old. Her mother's total cholesterol varied between 6 and 7 mmol/L. The patient's

blood pressure was 117/67 mmHg, BMI 23.8 kg/m² and the arterial pulses were symmetrical. We found no arcus cornealis, no xanthelasma, no Achilles tendon xanthomata, but probable tendinous xanthomata on both hands.

Presumptive FH was diagnosed based on her LDLc level at 14.6 mmol/L (Table 1). After a clinically negative but electrically positive ergometry, a coronary angiography revealed a three-vessel coronary heart disease and she underwent a coronary artery bypass graft (CABG). The medical treatment included acetylsalicylic acid 100 mg, clopidogrel 75 mg, rosuvastatin 20 mg, ezetimibe 10 mg once daily, and alirocumab subcutaneously every 2 weeks, and lowered LDLc to 3.8 mmol/L.

FH was confirmed with two distinct heterozygous missense *LDLR* mutations: c.81C > G/p.Cys27Trp (15–30% residual activity) and c.1646G > A/p.Gly549Asp (residual activity <2%) both classified as likely pathogenic (Hobbs, Brown, & Goldstein, 1992). No *APOB* or *PCSK9* mutation was found. Parents and siblings could not be sequenced, and chromosomal analyses were not performed. The complete status of *LDLR* mutations could not be formally confirmed, but based on the clinical presentation of very high LDLc and early atherosclerosis, we presume a compound heterozygous mutation with both missense mutations compromising *LDLR* activity.

As the patient was considering maternity, contraceptives were advised for at least 12 months after CABG. Preconception drug withdrawal was planned with a bridge to lipid apheresis (France et al., 2016; Ogura et al., 2016; Watts et al., 2015), such as the Direct Adsorption of Lipoproteins (DALI).

TABLE 1 Evolution of the lipid profile before, during, and after pregnancy

| Treatment | Before pregnancy | | Pregnancy | | Postpartum | |
|---------------------------|------------------|-----------------------------------|--------------------|---------------------|------------------|-----------------------------------|
| | FH diagnosis | FH full treatment | Gestational week 7 | Gestational week 10 | | At 3 months |
| | None | Three combined drugs ^a | | Before first DALI | After first DALI | Three combined drugs ^a |
| Total cholesterol, mmol/L | 17.0 | 5.7 | 5.3 | 9.6 | 5.7 | 6.3 |
| HDL-cholesterol, mmol/L | 2.6 | 1.3 | 1.3 | 1.3 | 1.1 | 1.1 |
| LDL-cholesterol, mmol/L | 14.6 | 3.8 | 3.7 | 7.9 | 4.3 | 4.7 |
| Triglycerides, mmol/L | 1.2 | 1.3 | 0.6 | 0.9 | 0.6 | 1.0 |
| Apolipoprotein A1, g/L | 1.13 | 1.34 | – | 1.26 | 1.08 | – |
| Apolipoprotein B, g/L | 3.80 | 1.12 | – | 2.15 | 1.28 | – |
| Lipoprotein (a), mg/L | – | 1,150 | – | 918 | 483 | – |

Abbreviations: DALI, direct adsorption of lipoproteins technique of lipid apheresis; FH, familial hypercholesterolemia; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

^aThe three drugs consisted of rosuvastatin 20 mg once daily, ezetimibe 10 mg once daily, and alirocumab 150 mg subcutaneously every 2 weeks.

However, an unplanned pregnancy occurred after 9 months. Except for acetylsalicylic acid, all oral medications were stopped 7 weeks after the last menstrual period and pregnancy multivitamins were introduced. The last dose of alirocumab was self-injected 16 days after the last menstrual period. To control the rising LDLc throughout pregnancy, DALI sessions were started and the interval was adapted between 4 and 10 days (Figure 1) according to pretreatment LDLc and the estimated mean LDLc with the Kroon formula (Kroon et al., 2000). DALI was performed through a tunneled cuffed internal jugular catheter with the Art Universal device (Fresenius Medical Care) using two 500-ml adsorbers in series. The circuit was primed with heparin, of which 1,500 IU were delivered to the patient, and clotting was prevented by regional citrate anticoagulation (ACD-A solution, 275 ml per session). Calcium gluconate was infused

continuously to prevent hypocalcemia. Hypovolemia related to the priming of lines and columns (total 580 ml) was prevented by NaCl 0.9% infusion. Each DALI session lasted an average of 145 min, processed 7.4 L of blood with a maximal blood pump flow of 60 ml/min.

2.1 | Complete agenesis of the corpus callosum detected in utero

First trimester ultrasound did not show signs of aneuploidy. The anatomy ultrasound at 20 gestational weeks suspected an isolated complete agenesis of the corpus callosum, later confirmed by fetal magnetic resonance imaging at 22 gestational weeks (Figure 2). The comparative genomics hybridization array (Agilent oligoNT array CGH 180 K) was normal.

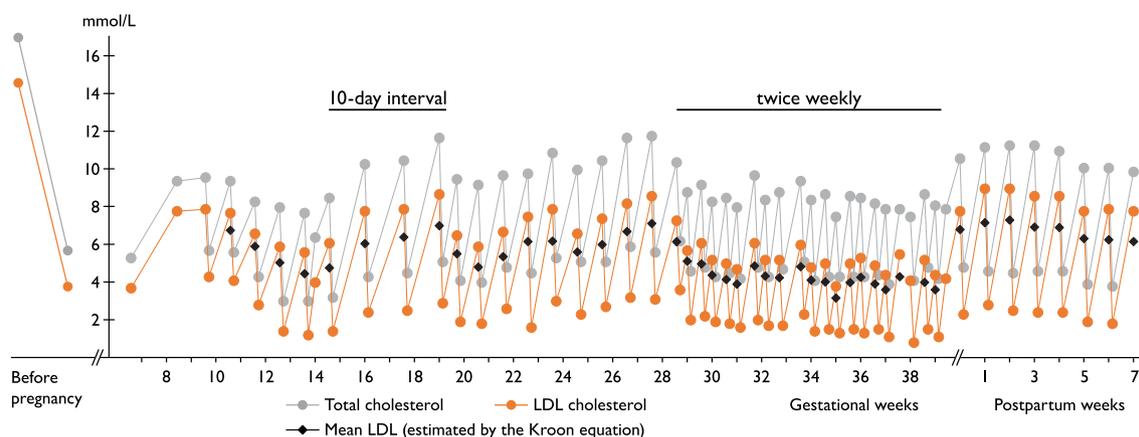


FIGURE 1 Evolution of the lipid profile during lipid apheresis. Before pregnancy (on the left of the y-axis), the total and LDL cholesterol (gray and orange circles, respectively) were reduced with the combined treatment of rosuvastatin 20 mg once daily, ezetimibe 10 mg once daily, and alirocumab 150 mg subcutaneously every 2 weeks. Last alirocumab injection was done 16 days after the last menstrual period and ezetimibe and rosuvastatin were stopped at seven gestational weeks after the pregnancy was confirmed (on the right of the y-axis). A complete agenesis of the corpus callosum was confirmed with a fetal MRI at 22 gestational weeks. During pregnancy and in the postpartum period, lipid apheresis sessions were performed at regular intervals to control total and LDL cholesterol (gray and orange). The interval between each session was adapted throughout pregnancy (every 7 days, unless stated otherwise in the figure) according to pretreatment LDLc and the estimated mean LDLc with the Kroon formula (Kroon, van't Hof, Demacker, & Stalenhoef, 2000)

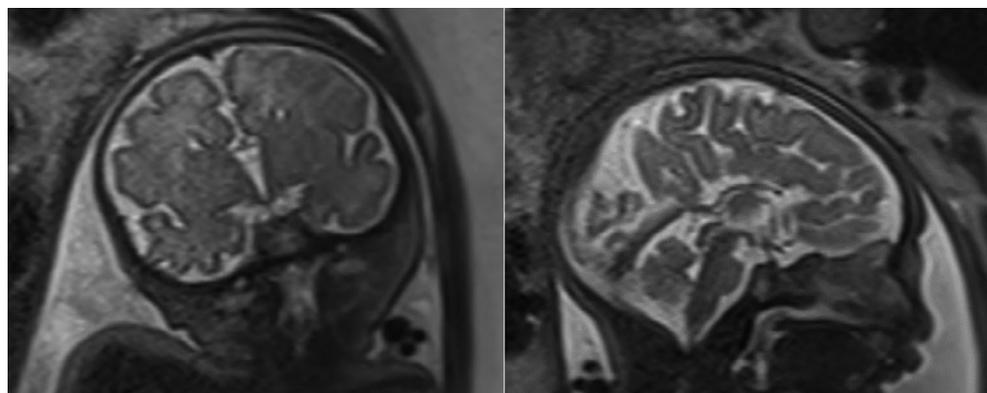


FIGURE 2 Fetal MRI (left panel, frontal; right panel, sagittal) realized at 22 gestational weeks

Cesarean delivery was performed at 40 gestational weeks, due to fetal bradycardia at 7 cm dilation after spontaneous labor. The male newborn had an Apgar score of 10–10–10, an arterial pH at 7.25, and venous pH at 7.31. The birth length was 49 cm (25th percentile), weight 3,220 g (50th percentile) and head circumference 35 cm (50th percentile), with normal clinical examination at birth.

The infant showed normal developmental milestones and neurological examination until the last clinical visit at 9 months of age. His LDLc was elevated at 3.5 and 5.0 mmol/L at 2 and 7 months, respectively. We could not find any exposure factors, in particular no toxic or alcohol before or during pregnancy.

3 | DISCUSSION

To our knowledge, this is the first report of exposure to PCSK9 inhibitors in early pregnancy. A causal link between the early pregnancy exposure to this drug (or statins and ezetimibe taken concomitantly) and the complete agenesis of the corpus callosum cannot be assessed based on a single case.

The accountability of the drugs in congenital midline defect can be considered unlikely for several reasons. First, the sensitive period for the corpus callosum development is probably not in the first 10 weeks of pregnancy. Based on the last use of the three lipid-lowering drugs and their half-lives, the exposure period did not extend beyond 10 weeks, even when accounting for the alirocumab half-life of 12 days (i.e., stopped at 16 days after the last menstrual period +4 half-lives expected to reach a 94% clearance leading to 9 weeks). Second, monoclonal antibodies are not considered to cross the placenta significantly before the second trimester (Pham-Huy et al., 2019). No specific data are available on monoclonal antibodies targeting PCSK9, such as alirocumab, but its placental transfer is not expected to differ dramatically from other monoclonal antibodies. Finally, recent data with a strong level of evidence on statins safety in pregnancy did not confirm the previously observed association between statins and teratogenic risks (Bateman et al., 2015; Botha, Pilcher, Wolmarans, Blom, & Raal, 2018).

Clinical guidelines do not recommend specific preconception measures to lower fetal and/or maternal risks of patients with severe FH considering pregnancy. Our patient reported good tolerance to lipid apheresis throughout pregnancy. We argue that lipid apheresis and other relevant measures should be discussed before pregnancy with women with FH on an individual basis, until large pharmacoepidemiology studies assessing the safety of PCSK9 inhibitors in pregnancy are available.

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The authors have nothing to disclose. The authors declare that all supporting data are available within the article. The patient reported here signed a written consent for this publication. The authors wish to thank the clinical team who cared for the patient during the DALI sessions and in clinic, as well as Dr. Nathalie Brun, Geneva University Hospitals, and Dr. Thomas von Kaenel, Valais Hospital, Switzerland, for their assistance in the genetic testing.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data available on request due to patient privacy restrictions.

REFERENCES

- Bateman, B. T., Hernandez-Diaz, S., Fischer, M. A., Seely, E. W., Ecker, J. L., Franklin, J. M., ... Huybrechts, K. F. (2015). Statins and congenital malformations: Cohort study. *BMJ (Clinical Research Ed.)*, *350*, h1035. <https://doi.org/10.1136/bmj.h1035>
- Botha, T. C., Pilcher, G. J., Wolmarans, K., Blom, D. J., & Raal, F. J. (2018). Statins and other lipid-lowering therapy and pregnancy outcomes in homozygous familial hypercholesterolaemia: A retrospective review of 39 pregnancies. *Atherosclerosis*, *277*, 502–507. <https://doi.org/10.1016/j.atherosclerosis.2018.05.038>
- France, M., Rees, A., Datta, D., Thompson, G., Capps, N., Ferns, G., ... HEART UK Medical Scientific and Research Committee. (2016). HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. *Atherosclerosis*, *255*, 128–139. <https://doi.org/10.1016/j.atherosclerosis.2016.10.017>
- Hobbs, H. H., Brown, M. S., & Goldstein, J. L. (1992). Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. *Human Mutation*, *1*(6), 445–466. <https://doi.org/10.1002/humu.1380010602>
- Kroon, A. A., van't Hof, M. A., Demacker, P. N. M., & Stalenhoef, A. F. H. (2000). The rebound of lipoproteins after LDL-apheresis. Kinetics and estimation of mean lipoprotein levels. *Atherosclerosis*, *152*(2), 519–526.
- Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimón, L., ... ESC Scientific Document Group. (2020). 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *European Heart Journal*, *41*(1), 111–188. <https://doi.org/10.1093/eurheartj/ehz455>
- Ogura, M., Makino, H., Kamiya, C., Yoshimatsu, J., Soran, H., Eatough, R., ... Stefanutti, C. (2016). Lipoprotein apheresis is essential for managing pregnancies in patients with homozygous familial hypercholesterolemia: Seven case series and discussion. *Atherosclerosis*, *254*, 179–183. <https://doi.org/10.1016/j.atherosclerosis.2016.10.018>
- Pham-Huy, A., Sadarangani, M., Huang, V., Ostensen, M., Castillo, E., Troster, S. M., ... Top, K. A. (2019). From mother to

baby: Antenatal exposure to monoclonal antibody biologics. *Expert Review of Clinical Immunology*, 15(3), 221–229. <https://doi.org/10.1080/1744666X.2019.1561282>

Thompson, G. R., Blom, D. J., Marais, A. D., Seed, M., Pilcher, G. J., & Raal, F. J. (2017). Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol. *European Heart Journal*, 39(14), 1162–1168. <https://doi.org/10.1093/eurheartj/ehx317>

Watts, G. F., Gidding, S. S., Wierzbicki, A. S., Toth, P. P., Alonso, R., Brown, W. V., ... International Familial Hypercholesterolemia Foundation. (2015). Integrated guidance on the care of familial hypercholesterolaemia from the international

FH foundation. *European Journal of Preventive Cardiology*, 22(7), 849–854. <https://doi.org/10.1177/2047487314533218>

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