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Pregnancy in homozygous familial hypercholesterolemia − Importance of LDL-apheresis

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Abstract

Introduction: Rare cases of pregnancy in women with homozygous familial hypercholesterolemia (HFH) have been reported. HFH might pose significant risks for the mother and her fetus. Statins, the most potent agents for low-density lipoprotein (LDL) cholesterol reduction, are contraindicated; thus lipoprotein apheresis remains the only effective treatment.

Case report: We report on a 34-year-old pregnant woman with HFH who was treated throughout the entire pregnancy by lipoprotein apheresis (immunoadsorption method). Increasing levels of LDL-cholesterol were stabilized at 9−10 mmol/L by lipoprotein apheresis (performed every 10 days). No complications were observed during the treatment procedures. Monitoring of the fetus revealed no impairment of the umbilical cord and blood flow in the uterine arteries, as well as no intrauterine growth retardation. The delivery was spontaneous and the child was breastfed for two months.

Conclusion: Intensive treatment by lipoprotein apheresis is an effective and safe therapeutic strategy during pregnancy, even in severe cases of HFH, as it can stabilize progressively increasing lipoprotein levels and prevent severe complications.

Keywords: Homozygous familial hyperlipoproteinemia; Pregnancy; Lipoprotein apheresis; Extracorporeal elimination; Therapeutic hemapheresis; LDL-cholesterol

1. Introduction

Familial hypercholesterolemia (FH), the most common and severe monogenic form of hypercholesterolemia, is an autosomal co-dominant disease characterized by increased plasma low-density lipoprotein (LDL)-cholesterol concentration [1]. In 85−90% cases, the disease is caused by mutations in the gene encoding for the LDL-receptor [2,3]. FH is associated with a substantially increased risk (as many as 20-fold) of premature atherosclerosis [4], with CHD affecting males in particular, as early as in their fourth decade of life and females 10−15 years later [5]. The incidence of the most severe homozygous form is low (1/1,000,000 individuals) [5] with mutations inherited from both parents and present in both alleles. Cholesterol levels are very high and can reach levels three to six times greater than the normal upper limit (12−30 mmol/L), while CHD symptoms can be observed even in early childhood and deaths of untreated patients younger than 20 years have been reported [6]. In severe cases of homozygous familial hypercholesterolemia (HFH), fatty-streaks in fetal aorta

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have been found [7]. Occasional extreme cases of HFH have been documented, including the death of a 4-year-old infant caused by heart attack [8] and bypass surgery was performed on a 13-year-old child due to CHD [9]. Thus, patients with HFH are at high risk of developing complications.

Pregnancy is a physiological, yet very demanding condition. It is well known that during pregnancy the organism undergoes major hormonal changes with fluctuations of cytokine and interleukin levels. Rapid growth of the child represents a metabolic as well as physical burden for the pregnant woman. The combination of HFH and pregnancy can be a fatal condition. In 1984, Kroon et al. reported that pregnancy in women with HFH is extremely rare and has a high mother and child mortality rate [10].

The prognosis of these patients has recently improved, however it still represents a serious medical problem with an estimated 30% possibility of acute coronary morbidity in mother or child [12].

In the literature, information on therapeutic management of pregnancy in HFH is only sparsely available and merely includes reports on single or small groups of patients. According to our estimation, approximately 25 cases have been published. Moreover, these case reports often contain incomplete information, omit important data or are not carried out according to standardized diagnostic procedures. These case reports also display inconsistencies in therapeutic details and the descriptions sometimes lack sufficient details. There is still the need for a targeted study following the rules of evidence-based medicine.

Patients with HFH are at risk of atherosclerosis, which is very often present during childbearing age. This might affect uteroplacental circulation leading to insufficiency, which could contribute to associated pregnancy complications [10]. Hemodynamic stress during pregnancy may exacerbate pre-existing cardiovascular lesions and precipitate acute events, to an extent that some report HFH as a possible contraindication for pregnancy in CHD [13]. Therefore, detailed preconceptional cardiovascular assessment should be performed in women who desire to become pregnant and this should guide their management.

During pregnancy, statins and ezetimibe are contraindicated, leaving lipoprotein apheresis as the only effective and generally accepted therapy. However, standardized guidelines for lipoprotein apheresis are still lacking. An individualized approach is necessary, as FH has a great phenotypic variability and the genotype–phenotype correlations are still poorly understood [14].

Problematic lactation is another difficult aspect of the disease. This complication is completely neglected in the published reports. There are basically two contending approaches: 1) Breastfeeding for the maximum possible time is beneficial for the child, however it is troubling for the mother (inconvenience with coordination of breastfeeding and frequent lipoprotein apheresis procedures) and can increase the risk of complications in the mother (risk of CHD progression in the mother due to high levels of lipoproteins without medical (drug) treatment). 2) Terminating lactation immediately after delivery and initiating treatment with statins and ezetimibe. However, the latter is also not very beneficial (not least for the child).

Here we report on a woman with familial FH and detail our therapeutic strategy and approach to lactation management.

2. Case report

We describe the case of a woman born in 1978 suffering from HFH (mutation: exon LDLR E10 + E12, type p.Asp492Asn/p.Gly592Glu). The baseline value of total cholesterol (TC) was 23 mmol/L upon therapy initiation in 1993. The patient often felt weak, tired and somnolent. She had xanthomas on her hands and Achilles tendons since her childhood and she needed to wear orthopedic shoes. Both parents had confirmed heterozygous FH. The diagnosis was first set in 1993 and although the patient had previously been examined at a regional hospital in order to determine her symptoms, cholesterol levels had not been analyzed. The patient was admitted to our Faculty Hospital in 1993 and we started regular plasma exchanges. After six months, the TC level dropped to 12 mmol/L and later to 10 mmol/L (Fig. 1). By April 4, 1994, the program of regular lipoprotein aphereses (immunoaphereses) was initiated and later, treatment with statins and ezetrol at maximal tolerated doses was added. TC and LDL-cholesterol (LDL-C) values of 5–6 mmol/L and 2.5–3.5 mmol/L, respectively, were achieved. Since 1995, the patient has exhibited no subjective symptomatology and xanthomas have been

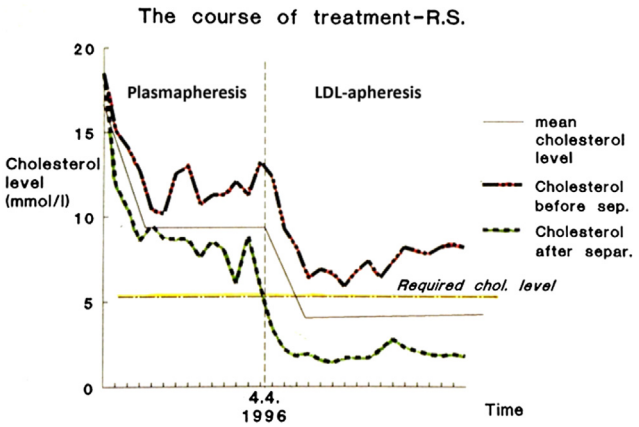

Fig. 1. Treatment of the patient between years 1993–1999. Legend: The chart schematically depicts the course of treatment. From 1993, plasma exchanges were performed repeatedly every two to three weeks. The cholesterol level decreased from baseline 18 mmol/L to average levels of around 10 mmol/L. On April 4, 1996, lipoprotein apheresis (immunoadsorption) treatment was initiated and performed in regular time intervals. The average cholesterol level was further reduced (chart shows the time period between years 1993 and 1999).

absent. The patient was in a completely physically fit condition and later found a job.

The treatment method: the therapy was started with plasma exchanges (1993–1996) – two thirds of one body volume of plasma (calculated by a blood cell separator computer) was replaced with 5% albumin and the rest with crystalloids (Ringer's or Hartmann's solution). In 1996, immunoadsorptions were initiated with plasma separation using a continuous separator (Cobe Spectra or Spectra Optia, Terumo BCT, USA) followed by flow of the plasma through a pair of adsorbers placed in an automated adsorption-desorption device (Adasorb, Medicap, Germany). We used Lipopak adsorber columns (Pocard, Moscow, Russland), designed for multiple use with sheep antibody against apolipoprotein B covalently bound to sepharose. The columns work in pairs and plasma flows through one of them. When the first column becomes saturated with LDL-C, the Adasorb device switches the flow to the other column while the first one is regenerated and the adsorbed cholesterol is flushed out by regeneration solutions (saline, glycine, PBS buffer) and prepared for further use. These cycles are repeated until the desired LDL-C level is achieved. The flow is continuous and the volume of washed plasma is determined by the level of LDL-C. Software calculates the optimal volume of plasma for saturation of the adsorption column for the specific LDL-C level. The optimal aim of the procedure is to reduce the LDL-C level to 1 mmol/L. During a single procedure, 6000–8000 ml of plasma is usually purified. Peripheral venous access was used and the procedures lasted for 4–5 h, depending on venous blood flow. Anticoagulation was provided in combination with heparin (bolus 3500 U i.v. followed by continuous ACD-A 1:15).

The patient became pregnant in April 2012. Due to the preceding intensive medical and lipoprotein apheresis treatments, lipoprotein levels were stabilized. Statin and ezetimibe administration was discontinued, but lipoprotein apheresis continued every 10 days until the delivery. The cholesterol-lowering diet remained unchanged. Cardiologic examination revealed suspicion of early atherosclerotic plaque on the aortal stem. As we were aware of case reports describing severe complications, possible rapid worsening of CHD, eventually leading to death of the child or mother, we put every effort into monitoring the patient, including repeated ultrasound examinations by a specialist and flow control through the umbilical cord and uterine vessels. The pregnancy proceeded without any problems, the patient continued with her job, and all monitored parameters (biochemical, hematologic and US) were normal except for mild anemia.

Levels of lipoproteins progressively increased from the beginning of the pregnancy. In the second trimester of pregnancy, the TC level stabilized at around 12 mmol/L and LDL-C at around 9 mmol/L (Fig. 2). In the first days after the delivery, TC increased and reached its highest value of 20.05 mmol/L (LDL-C: 15.55 mmol/L). In the following weeks after the delivery, levels of TC and LDL-C decreased and tended to decrease further. After 3 months, TC and LDL-C levels were 4.68 and 2.71 mmol/L, respectively.

Results of the gynecological observations: Careful follow-up procedures were carried out in an out-patient department because of the risk to the pregnancy. First, the patient was followed-up every three weeks and from week 38, CTG fetus monitoring was performed. Flow through the umbilical cord, uterine arteries and the child's growth showed normal development.

In week 39, she gave birth to a healthy boy and the delivery was smooth and spontaneous. The baby's birth weight was 2890 g and its development was normal. Both mother and child have been doing well so far.

The lactation plan was set upon agreement with the mother: lipoprotein apheresis procedures and breastfeeding were continued after the delivery. Lactation proceeded without complications and by the end of the second month, supplementary feeding was added to facilitate breastfeeding termination. Therapy, in the form of statins and ezetimibe, was reintroduced 3 months after the delivery.

3. Discussion

Pregnancy in women with familial hypercholesterolemia is rare and can be a critical challenge for both mother and fetus [15,16]. Current knowledge on physiological and pathophysiological conditions during pregnancy allows us to understand the troubling and dangerous situation, which may occur in patients with HFH. These patients usually experience clinically significant complications of atherosclerosis, particularly health-endangering CHD, as early as when they reach the age of peak fertility. Thus, coronary insufficiency may be further deteriorated by hemodynamic changes (both increased circulation rate and enlarged erythrocyte volume occur during pregnancy) and by extremely high cholesterol levels reached during pregnancy [1]. Elevated lipoprotein levels can be associated with uteroplacental vascular resistance and intrauterine growth restriction [17,18]. Increased lipoprotein levels contribute to the slowing of blood flow in umbilical vessels, which is a risk factor for fetal development retardation [12,19,20]. Impairments of lipoprotein metabolism, oxidative stress and reduced antioxidant defence enhance free radical-mediated membrane lipid peroxidation, possibly causing vascular endothelial damage and leading to a pre-eclamptic state, a very serious clinical condition manifested by hypertension, oedema and proteinuria [16,20,21].

Lipoproteins are not the only risk factors. It is well known that fibrinogen levels are increased during pregnancy, representing another risk factor for atherosclerosis development. Although hyperfibrinogenemia was not present in our patient, it must be mentioned as, according to our previous study on different microcirculation disorders, high fibrinogen levels are associated with increased blood and plasma viscosity and impaired perfusion of various

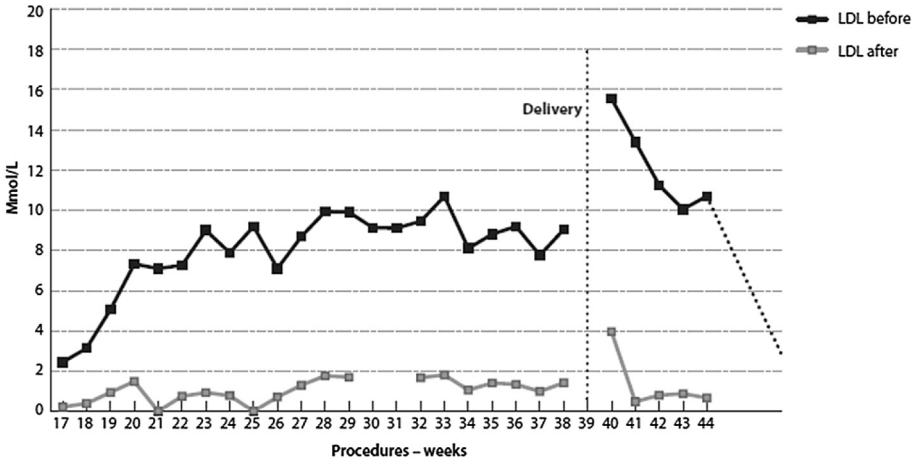

Fig. 2. LDL-C levels during pregnancy. Legend: LDL before – LDL-C level before the lipoprotein apheresis; LDL after – LDL-C level after the lipoprotein apheresis.

organs [22]. Increased viscosity is accompanied by other microcirculation alterations, including enhanced erythrocyte aggregability and associated flexibility [12,23]. It is possible that similar changes can also appear during pregnancy in FH.

According to Anedda et al., 2011, pregnancy increases the predisposition of the mother to atherosclerosis after delivery and later in life, as well as a risk of cardiovascular disorders in the offspring [16].

Unfavorable pathophysiological prerequisites culminate toward the end of the pregnancy when lipoprotein levels are markedly increased, other pathophysiological changes are present and the fetus reaches its maximum size. Therefore, during the last trimester, we monitored the patient every two weeks, including inspection of blood flow rates (umbilical cord, umbilical vessels, etc.), in order to be ready for immediate medical assistance in case of severe deterioration. Ultrasound examinations revealed that the pregnancy was on a satisfactory course and there was no need for special therapeutic intervention.

The initial stages of pregnancy are complicated by difficulties in therapeutic planning, as there are no rigorous rules for the treatment process. In addition, medical teams usually lack sufficient experience, technical and administrative problems may surface and there can be difficulties in communicating with insurance companies. This is also a challenging situation for the patient due to frequent visits, relatively long procedure times in the center, commuting distances to and from the center, etc. From a technical point of view, it is not really difficult to choose a method for extracorporal elimination of lipoproteins, as all existing techniques (HELP, DALI, double plasma filtration, dextran-sulfate adsorption, immunoadsorption) are suitable and effective [24,25]. The decisions are usually based on experience and the technical possibilities of individual centers.

As a result of our experiences, we agree with authors who consider lipoprotein apheresis a suitable therapeutic option for pregnant women with HFH [5,10–12,15,16]. It offers the only possibility of effectively lowering the level of LDL-C in pregnant HFH patients and reduces the risk of complications [25]. Different views exist on therapy timing and intensity (frequency). Due to the low frequency of these cases, there are no proven therapeutic guidelines. However, common rules applied during the years of HFH treatment by lipoprotein apheresis (in non-pregnant patients) are applicable. It is obviously beneficial to also continue the treatment of women undergoing regular lipoprotein apheresis before and during pregnancy with a frequency that maintains LDL-C at relatively low levels, according to individual patients. This usually means one procedure per one to two weeks to maintain acceptable levels of LDL-C. If lipoprotein apheresis treatment is initiated only at the beginning of the pregnancy, it is appropriate to start as soon as possible and continue throughout the entire pregnancy. Unfortunately, reluctance to perform extracorporeal treatment during pregnancy, even in patients undergoing regular apheresis therapy, is common among physicians [16]. The level of LDL-C had increased in our patient, but stabilized at a level of around 10 mmol/L, which allowed lipoprotein apheresis to be performed once every 10 days until the end of the pregnancy. These procedures had no adverse effects and the patient tolerated them very well.

In the literature, we found no information or concrete recommendations on lactation periods. Of the two above mentioned options – either interrupting the lactation immediately after the delivery or maintaining the lactation until its spontaneous end – we chose the “middle path,” which recommends continued breastfeeding while trying to maximally help the patient to manage the situation (see above). No problems occurred during the lactation period. In the third month, we made an effort to gradually cease lactation and to switch to supplemental child food. Immediately after the completion of lactation, treatment with statins and ezetimibe was resumed. The patient continued

with her strict diet and active lifestyle. We consider the presented management of the lactation period as the most appropriate, as long as the mother consents and collaborates.

As a result of summarizing the experience published in the literature and from our own experience, we conclude it is clear that pregnancy in homozygous FH represents a high risk for health, although the prognosis has recently improved due to advances in medical care. Currently, the need to categorically disallow or interrupt pregnancy is rare (see older views – [13]). The baseline situation is important; therefore, it is crucial to achieve optimal compensation for pre-existing (particularly cardiovascular) disorders before the planned pregnancy, or at least at its beginning, to ensure that all technical and economical conditions for lipoprotein apheresis are available in a timely manner. Lipoprotein apheresis is suitable immediately after the pregnancy begins (when the effective medication is discontinued). The aim is to maintain the LDL-C level at target values; however, this can be very challenging. The troubling problems for the patient are issues of high frequency and the length of the procedures. The most realistic, achievable interval between two procedures is one week. After a thorough consideration of our patient's situation (disease status, personal situation, demands of the patient), we decided to maintain the LDL-C level at least below 10 mmol/L and succeeded with the frequency of one lipoprotein apheresis every 10 days. Patients have to be carefully monitored and specialized medical personnel must be ready for an acute intervention in case of deterioration (particularly dangerous are cardiovascular complications and impaired development of the fetus, especially towards the end of the pregnancy). In the light of current knowledge, it is not possible to draw resolute and accurate conclusions in the sense of evidence-based medicine, because no prospective, controlled studies are available and that will most probably not change in the near future [2,20]. Nevertheless, according to published case reports, case series [1,2,5,10,11,13,16,20,25], review articles [2,12] and from our own experience, lipoprotein apheresis is the only option for maintaining LDL-C levels in HFH patients during pregnancy at acceptable values, while also providing a safe and technically well-executed method.

4. Conclusion

Lipoprotein apheresis is an effective therapeutic option for treatment of homozygous familial hyperlipoproteinemia during pregnancy. After individual risk/benefit analysis for mother and child, lipoprotein apheresis may be safely continued and acutely performed. Moreover, this technique does not interfere with the physiological adaptations of lipoprotein metabolism during pregnancy and may prevent potential superimposed complications such as placental insufficiency.

Conflict of interest

M. Blaha, M. Lanska, V. Blaha, L. Boudys and P. Zak have nothing to declare.

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