Clomiphene citrate–induced severe hypertriglyceridemia

Hamiyet Yılmaz Yaşar, M.D.,[a] *and Özden Ertuğrul, M.D.*[b]

[a] Department of Endocrinology; and [b] Department of Biochemistry, Aydin State Hospital, Aydin, Turkey

Objective: To report a case of severe hypertriglyceridemia associated with clomiphene citrate (CC) treatment.
Design: Case report.
Setting: A patient referred to an endocrinology clinic of a state hospital.
Patient(s): A 29-year-old, overweight woman with a history of polycystic ovary syndrome who had been given clomiphene citrate (CC) for ovulation induction and presented with severe hypertriglyceridemia. She had a family history of type 2 diabetes and hyperlipidemia.
Intervention(s): Clomiphene citrate treatment was discontinued, and gemfibrozil treatment at a dose of 1,200 mg/d was started.
Main Outcome Measure(s): Serum lipid levels.
Result(s): With the discontinuation of CC treatment and start of a specific lipid-lowering agent, the patient's lipid profile improved. After 3 months, CC therapy was restarted, and again severe hypertriglyceridemia developed, which resolved with the previous treatment strategies.
Conclusion(s): Clomiphene citrate should be used cautiously in women having risk factors for dyslipidemia, and, even in the presence of a normal lipid profile, lipid levels should be closely monitored when CC treatment is instituted. (Fertil Steril® 2009;92:396.e7–e8. ©2009 by American Society for Reproductive Medicine.)

Key Words: Hyperlipidemia, clomiphene, polycystic ovary syndrome

There are only two reported cases of clomiphene citrate (CC)–induced hyperlipidemia (1, 2). Clomiphene citrate is a nonsteroidal estrogen analogue that is used in the treatment of certain anovulatory disorders (3). It is believed to initiate ovulation by blocking endogenous estrogen feedback at the level of the hypothalamus, thereby promoting the release of LH and FSH (4). Clomiphene citrate, tamoxifen, and toremifene are all triphenylethylene plasma derivatives and are structurally similar (5). Although the effects of tamoxifen on lipid metabolism are well studied and described (4, 6, 7), the effects of CC on lipid metabolism are not clear. To our knowledge this is the third case reported about CC-induced severe hypertriglyceridemia. As different from the other reported cases, baseline lipid levels were normal and CC-induced hypertriglyceridemia was much more severe in our case.

CASE REPORT

A 29-year-old woman was referred to our clinic for severe hypertriglyceridemia. She had a history of polycystic ovary syndrome for which she had been treated with metformin at a dose of 850 mg twice a day. Because she desires pregnancy, she consulted her gynecologist. In March 2008 two cycles of CC were started at a dose of 100 mg/d. In June 2008 she presented to a local health care center for routine biochemical evaluation, and her triglyceride level was found to be >1,000 mg/dL. Therefore she was immediately referred to our clinic. She had no complaints when she was admitted to our clinic. She did not have abdominal pain, nausea, vomiting, or any other signs of pancreatitis. Physical examination results were normal except for her being overweight. Body mass index was 26.8 kg/m^2, and she had an upper body fat distribution. Laboratory testing showed normal transaminase, amylase, and lipase levels. Total cholesterol level was 314 mg/dL, low-density lipoprotein (LDL) cholesterol level was 63 mg/dL, triglyceride level was 12,622 mg/dL, and high-density lipoprotein (HDL) cholesterol level was 31 mg/dL. Clomiphene citrate was discontinued, and gemfibrozil treatment was started at a dose of 600 mg twice a day. She was recommended to have a low-fat diet (daily fat intake to be approximately <20% of the total energy) and to exercise. After 2 weeks of diet, exercise, and gemfibrozil therapy, her triglyceride level was decreased to 64 mg/dL, LDL cholesterol level was 113 mg/dL, total cholesterol was 181 mg/dL, and HDL cholesterol was 39 mg/dL. With this treatment she lost 5 kg in 3 months and her lipid levels remained in normal limits. In October 2008, CC treatment was restarted and gemfibrozil therapy was discontinued. However, she followed her diet and continued to exercise. In December 2008, when she

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Reprint requests: Hamiyet Yılmaz Yaşar, M.D., Aydin State Hospital, Department of Endocrinology, Aydin, Turkey (FAX: 00-90-256-225-46-20; E-mail: drhamiyetyilmaz@yahoo.com).

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was checked for lipid levels, her triglyceride level was found to be 5,100 mg/dL, total cholesterol level was 250 mg/dL, LDL cholesterol level was 153 mg/dL, and HDL cholesterol level was 41 mg/dL. A diagnosis of CC-associated hypertriglyceridemia was made, and CC was stopped. Then she was given retreatment with gemfibrozil along with diet therapy. After 2 weeks of therapy lipid levels returned to normal limits. Thereafter she consulted with her gynecologist because of this hypertriglyceridemic effect of CC therapy, and alternative therapy with recombinant human FSH and LH was recommended. Also the patient was told that pregnancy might exacerbate hypertriglyceridemia, and the patient decided to postpone the fertility treatment.

DISCUSSION

Clomiphene citrate has been used for ovulation induction in the treatment of infertility since 1960 (3). It has mixed agonistic-antagonistic properties. Acting as an antiestrogen, CC is believed to displace endogenous estrogen from hypothalamic estrogen receptors, thereby removing the negative feedback effect exerted by endogenous estrogens. The change in pulsatile LH-releasing hormone release is thought to normalize the release of pituitary FSH and LH and initiates ovulation (8).

Although the effects of estrogen and synthetic estrogen analogues on lipids are well described, the effects of CC on plasma lipids are not well studied. Despite its common use in anovulatory disorders, there are only two reports about severe hypertriglyceridemia induced by the use of this medication (1, 2).

Estrogen has been shown to decrease total and LDL cholesterol concentrations and increase HDL cholesterol and triglyceride levels. Newer selective estrogen receptor modulators such as raloxifene have a favorable effect on lipid profile by decreasing LDL cholesterol levels (9). It does not affect triglyceride levels in nonobese women (10). Tamoxifen, which is structurally similar to CC and toremifene (triphenylethylene derivative), is being used in the treatment of breast cancer as an adjuvant therapy (1, 2). Its effect on lipid metabolism has been well studied (6, 11). Tamoxifen, like estrogen, decreases total and LDL cholesterol levels, but, unlike estrogen, it has little effect on HDL cholesterol. It also may increase triglyceride concentrations especially in patients with underlying familial hypertriglyceridemia (1, 2, 12). This effect on lipid metabolism may be due to its estrogen-like actions. Estrogen induces hepatic very low density lipoprotein synthesis and at the same time inhibits lipoprotein lipase action, resulting in increased secretion, as well as decreased clearance, of very low density lipoprotein particles (12, 13). Therefore the possible mechanism of tamoxifen' s effect on triglyceride levels is by reducing the activity of lipoprotein lipase and hepatic triglyceride lipase (2). Toremifene also has an adverse effect on triglyceride concentrations. In rats CC increased plasma cholesterol concentrations, but there is no information about the effect on triglyceride levels (14). However, its effect on lipid metabolism in humans is not well studied. It is suggested that, because it is structurally similar to tamoxifen, it can cause hypertriglyceridemia by a similar mechanism (2). Hypertriglyceridemia may be severe especially in patients with genetic abnormalities such as mutations of the LPL or APOE gene (1). To our knowledge this is the third case report of severe hypertriglyceridemia caused by the use of CC. In the previous two reports the patients already had mild hyperlipidemia before the onset of CC treatment. However, our patient had a normal baseline lipid profile, in spite of having a history of polycystic ovary syndrome and a family history of combined hyperlipidemia as risk factors for hyperlipidemia before CC therapy. After the onset of CC therapy, severe hypertriglyceridemia was established. The patient was informed about the risk of hypertriglyceridemia during pregnancy, and she decided to postpone the treatment for ovulation induction.

In conclusion, serum lipid levels should be measured for patients having risk factors predisposing to hyperlipidemia before ovulation induction with CC. Even if the lipid levels are normal, lipid profile should be followed up closely. In case of deterioration of the lipid profile, CC treatment should be ceased immediately, and alternative therapy for ovulation induction should be recommended.

REFERENCES

1. Gillet MJ, Burnett JR, Yeap D. Clomiphene-associated combined hyperlipidemia. J Reprod Med 2006;51:587–90.
2. Castro MR, Nguyen TT, O'Brien T. Clomiphene-induced severe hypertriglyceridemia and pancreatitis. Mayo Clin Proc 1999;74:1125–8.
3. Seibel MM, ed. Infertility: a comprehensive text. Norwalk, CT: Appleton & Lange, 1990.
4. Baker VL, Jaffe RB. Clinical uses of antiestrogens. Obstet Gynecol Surv 1996;51:45–9.
5. Morello KC, Wurz GT, DeGregorio MW. SERMs: Current status and future trends. Crit Rev Oncol Hematol 2002;43:63–76.
6. Love RR, Wiebe DA, Newcomb PA, Cameron L, Leventhal H, Jordan VC, et al. Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. Ann Intern Med 1991;115:860–4.
7. O'Brien T, Nguyen TT. Lipids and lipoproteins in women. Mayo Clin Proc 1997;72:235–44.
8. Adashi E. Clomiphene citrate–initiated ovulation: a clinical update. Semin Reprod Endocrinol 1986;4:225–76.
9. Walsh BW, Kuller LH, Wild RA, Paul S, Farmer M, Lawrence JB, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. JAMA 1998;279:1445–51.
10. Mosca L, Harper K, Sarkar S, O'Gorman J, Anderson PW, Cox DA, et al. Effect of raloxifene on serum triglycerides in postmenopausal women: influence of predisposing factors for hypertriglyceridemia. Clin Ther 2001;23:1552–65.
11. Hozumi Y, Kawano M, Saito T, Miyata M. Effect of tamoxifen on serum lipid metabolism. J Clin Endocrinol Metab 1998;83:1633–5.
12. Hozumi Y, Kawano M, Miyata M. Severe hypertriglyceridemia caused by tamoxifen treatment after breast cancer surgery. Endocr J 1997;44:745–9.
13. Keilson LM, Vary CPH, Sprecher DL, Renfrew R. Hyperlipidemia and pancreatitis during pregnancy in two sisters with a mutation in the lipoprotein lipase gene. Ann Intern Med 1996;124:425–8.
14. Turner RT, Evans GL, Sluka JP, Adrian MD, Bryant HU, Turner CH, et al. Differential responses of estrogen target tissues in rats including bone to clomiphene, enclomiphene and zuclomiphene. Endocrinology 1998;139:3712–20.