Gestational Severe, Nonfamilial Hypertriglyceridemia, Management with Insulin and Metformin, A Case Report

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Abstract
Severe hypertriglyceridemia is a rare condition in pregnancy. We report a case of gestational, nonfamilial severe hypertriglyceridemia accompanied with gestational diabetes mellitus. Despite an intensive insulin regimen and dietary fat restriction plasma triglyceride levels were remained higher. After a plasmapheresis session, triglyceride levels were reduced nearly 40%. Since plasma glucose and triglyceride levels were higher, metformin therapy was administered. After two weeks of metformin therapy, plasma glucose levels were within target range and triglyceride level was reduced below 1000 mg/dl. She delivered at 38th week of pregnancy via elective cesarean section, a healthy female baby with normal birth weight. Serum triglyceride level decreased immediately to 280 mg/dl after delivery.

Keywords: Gestational diabetes; Hypertriglyceridemia; Metformin

Introduction
It is well known that plasma lipid levels increase during pregnancy because of increased levels of estrogen, progesterone, and human placental lactogen. However, expected elevations for triglyceride (TG) and total cholesterol levels during a normal gestational period usually do not exceed 332 mg/dl and 337 mg/dl, respectively, in uncomplicated pregnancies (1). Here, we present a report of 32 years old woman with gestational non-familial, severe hypertriglyceridemia accompanied with gestational diabetes mellitus.

Case Report
A 32 year old woman was admitted to our department at 27th week of her first pregnancy. She was diagnosed as gestational diabetes mellitus after a 75 gm glucose loading test and recommended of dietary restriction of glucose. She had complaint of mild headache and fatigue. Neither abdominal pain, nor nausea and vomiting was reported. No clinical signs, suggestive of hyperlipidemia, such as tendinous xanthomata, lipemia retinialis or other skin lesions were detected. She had a slightly increased level of triglyceride (240 mg/dl) and normal cholesterol level, one year before pregnancy and she had no relevant family history. Her Body Mass Index (BMI) was 27.9 kg/m² before pregnancy, and she gained 10 kg during past two trimesters. Serum lipoprotein profile revealed following findings: TG: 15,600 mg/dl (75-220); total cholesterol: 459 mg/dl (120-220); high density lipoprotein cholesterol (HDL-C): 43 mg/dl (40-65). Amylase and lipase levels were within normal limits. Abdominal ultrasound imaging was unremarkable with absence of cholelithiasis and all antenatal obstetrical evaluation were normal. Fasting plasma glucose was 126 mg/dl, thyroid, liver and renal function tests were normal. An overnight refrigeration serum sample revealed turbid appearance suggesting the presence of increased Very Low Density Lipoprotein (VLDL) fraction. Intensive insulin therapy and Low Molecular Weight Heparin (LMWH) were administered with medical nutrition therapy (dietary restriction of carbohydrates and fat (20 gr per day)). After seven days of treatment despite high doses of insulin (80 IU/day), blood glucose levels were still above the normal limits and triglyceride level was 12,300 mg/dl. Metformin therapy was started to improve glucose sensitivity and lower triglyceride levels at 850 mg/doses once a day and titrated to three times a day. After five days of metformin blood glucose was decreased within the target range while TG level was remained higher despite a significant reduction (TG= 6200 mg/dl). A therapeutic lipid apheresis, targeting a TG level below 1,000 mg/dl, for preventing acute pancreatitis was performed. After one session of lipid apheresis which was very painful for the patient TG levels fell from 6,200 mg/dl to 3460 mg/dl. The following day we suggested an additional apheresis session but she did not approved. She did not tolerate omega -3 fatty acids. Thus, she was treated with intensive insulin therapy, metformin, medical nutrition, exercise and LMWH with close monitoring of plasma triglycerides. Her TG levels ranged from 550 mg/dl to 880 mg/dl until delivery. She delivered at 38th week of pregnancy via elective cesarean section a healthy female baby with normal birth weight. Serum TG level decreased immediately to 280 mg/dl after delivery.

Discussion
Gestational severe hypertriglyceridemia (HTG) is a very rare disorder with life threatening complications, such as acute pancreatitis, hyperviscosity syndrome and preeclampsia, if left untreated [1,2]. Pregnancy, induces severe hyperlipoproteinemia, due to estrogen-induced increase in lipoprotein production and decrease lipoprotein lipase activity in the liver and adipose tissue. The highest level of triglyceride is observed in the third trimester and may rise up to 2-4 times above normal [3-5]. But for most women with normal baseline TG levels and without abnormality in metabolic pathways, such increases are well tolerated. Risk factors for gestational hypertriglyceridemia include the following conditions; obesity, weight gain, hypothyroidism, gestational or nongestational diabetes mellitus, alcohol intake, glucocorticoids and anticonvulsant drugs [6]. Our patient had three of these risk factors that were obesity, weight gain and gestational diabetes mellitus. However, data regarding the association of diabetes mellitus (gestational or
pregestational) and hypertriglyceridemia are conflicting. While some experts report a significant association [7-9] others not [10,11]. Underlying genetic mutations including dysbetalipoproteinemia, partial lipoprotein lipase (LPL) deficiency, and ApoE3/3 genotype are also important risk factors for gestational hypertriglyceridemia [12]. However, in carriers of genetic diseases such as LPL deficiency and dysbetalipoproteinemia, pregestational triglyceride levels usually above 1000 mg/dl and above 500 mg/dl, respectively [6,13]. Near normal triglyceride levels in our patient, in the pregestational and postpartum period may rule out the possibility of partial LPL deficiency with or without apoE3/2 or apoE4/2 genotype. Most causes of HTG are attributable to familial HTG, but nongenetic nonfamilial pregnancy-induced HTG in a patient has been reported previously [14]. However, she had a pancreatitis attack due to severe hypertriglyceridemia, two years before pregnancy, and had a family history of early atherosclerosis. Thus, our patient is unique because of clear data suggest the occurrence of gestational, non familial severe HTG. As we stated above, severe HTG in pregnancy has to be treated immediately to prevent acute pancreatitis and hyperviscosity syndrome. A very low-fat diet, defined by dietary fat below 20% of caloric intake, is the mainstay of clinical management of severe hypertriglyceridemia [15]. There are strong evidence that suggest prepregnancy BMI is an important determinant of many pregnancy outcomes. However, the committee recommend that weight loss should be addressed preconceptionally, not during pregnancy, because the safety of intentional weight loss during pregnancy has not been determined [16]. Further reports of severe hypertriglyceridemia during pregnancy have described various other management strategies, including fibrates, omega 3 fatty acids, heparin, intravenous insulin/glucose, parenteral feeding, plasmapheresis and low-density lipoprotein/apoE [15]. However, data regarding association of statins and teratogenity are limited, it is not recommended to use them during pregnancy [17]. Indeed, statins are still formally contraindicated during pregnancy as categorised X, by FDA. Lipophilic statins (lovastatin, simvastatin) have the most experience and therefore have more evidence related to teratogenic potential. In addition, there is no data for rosuvastatin and pitavastatin regarding their use in pregnancy. Further evaluation is required to assess the possible differences in risk between individual statins [18]. Although, fibrates are contraindicated in pregnancy, there have been a few case reports of the successful use of gemfibrozil, during pregnancy with no side effects particularly in the third trimester [19,20]. Metformin improves insulin resistance, and it has been suggested that it influences plasma lipids, independent of glycemic control [21]. In type 2 diabetes, metformin treatment is associated with a reduction in plasma triglyceride, total cholesterol, LDL cholesterol, and VLDL cholesterol concentrations [22]. Moreover, metformin (pregnancy category, B) has been considered as a potentially effective drug in management of gestational diabetes mellitus [23]. However, there is no evidence to suggest the use of metformin in gestational hypertriglyceridemia, yet. To date, our patient is the first published case of non familial gestational severe hypertriglyceridemia treated with metformin successfully. In conclusion metformin seems to be a safe drug in pregnancy and it worked very well in our case of severe HTG accompanied with gestational diabetes mellitus.

References