Case report

Preventive Management of Hypertriglyceridemia in Pregnancy
--A Case Report

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ABSTRACT

Background: Hypertriglyceridemia in pregnancy is a rare but well-known cause of hypertriglyceridemia-induced acute pancreatitis (HTGP) in pregnancy, a life-threatening condition that lacks an established guideline for treatment management.
Case presentation: We report a case with a successful treatment management of hypertriglyceridemia in pregnancy. A pregnant woman had been with hypertriglyceridemia for more than seven years and a history of pregnancy termination due to the development of HTGP. Eleven months after her last pregnancy termination, the woman was pregnant again and she started managing her elevated levels of lipids in the second trimester throughout the pregnancy, with low molecular weight heparin and then combined with metformin, to regulate the lipid metabolism and prevent thrombosis.
Results: The entire pregnancy progressed smoothly, and the triglycerides' level fluctuated during the second and the third trimester of pregnancy with a range of 16.15 to 47.65 mmol/L. A full-term delivery, with a reasonable outcome for both mother and newborn, was obtained. Compared with her last pregnancy, the outcomes of recent pregnancy were better off.
Conclusion: Low molecular weight heparin combined with metformin can avoid maternal hypertriglyceridemia-induced pancreatitis in this single case. To our knowledge, such a combination of treatment management of patients with hypertriglyceridemia in pregnancy to prevent acute pancreatitis has not been reported previously.

KEYWORDS

Metformin; low molecular weight heparin; hypertriglyceridemia in pregnancy; hypertriglyceridemia-induced pancreatitis.

INTRODUCTION

Pregnancy-related hyperglyceridemia is a rare but well-known cause of hypertriglyceridemia-induced acute pancreatitis (HTGP) in pregnancy. In general, gallstones and alcohol abuse cause more than 60-75% of acute pancreatitis, while hypertriglyceridemia may account for up to 15% of acute pancreatitis, similar in both males and females(1-3), and it is associated with severity of acute pancreatitis. The acute pancreatitis in pregnancy was rare at about 3 cases per 10,000 pregnancies (3), and the maternal and fetal mortality has dropped to 0-3% (4, 5). However, HTGP contribute to the majority of deaths in patients with acute pancreatitis in pregnancy. When serum triglyceride (TG) is elevated to or above 11.3 mmol/L (i.e., 1000mg/L), the risk of developing acute pancreatitis may increase significantly (6). HTGP can develop in the second but more commonly in the third trimester of pregnancy, and it is acute onset, with more complications and recurrent episodes.

Women, when pregnant, tend to have a significant increase in lipids and lipoprotein. Elevated levels of total cholesterol, low-density lipoprotein cholesterol (LDL), triglyceride (TG), and high-density lipoprotein cholesterol (HDL) are often observed in the second or third trimester (7, 8). The

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leading cause of hyperlipidemia is pregnancy-induced changes in hormones such as progesterone, estrogen, and 17a-hydroxyprogesterone (17a-OHP) (9), and their effect on target organs can lead to gestational diabetes or hypertension. Therefore, the pregnancy-related elevation of lipids in the blood is more difficult to be controlled. A high level of triglyceride is the cause of developing pancreatitis (10). Once the conditions of hypertriglyceridemia are developed, the traditional treatment is less effective than that for other types of pancreatitis.

Clinically, there have no established guidelines for the management of HTGP. Once complicating with HTGP in pregnancy, a pregnant woman may face some life threats, termination of pregnancy is an option to treat HTGP (11). However, a fetus of fewer than 28 weeks tends to have a lower survival rate. The clinical value of preventive measures may be far important than the pharmacological treatment of HTGP or termination of pregnancy. Here we report a case of a pregnant patient with hypertriglyceridemia who had a history of termination in her past pregnancy due to HTGP; the patient had interventional management with low molecular weight heparin (LMWH) combined with metformin during the second pregnancy and achieved a reasonable outcome. The study was approved by the Ethics Committee of the second XiangYa Hospital of Central South University and the patients provided informed consent.

CASE PRESENTATION

A 33-year Chinese woman developed HTGP in her last pregnancy. The pregnant woman did not have regular clinical visits to maternal health care during her last pregnancy, so dyslipidemia was not found promptly, and then led to the development of HTGP; the pregnancy ended with an induced abortion in the 23rd weeks of gestation. At that time, the blood level of triglyceride (TG) was up to 97.17 mmol/L, and the level of D-dimer was also elevated compared with pregnant women in similar gestational weeks. The dyslipidemia condition was serious at the time of onset and was with complications. Some conservative treatments seemed not working well, and the gestational week was small. The patient and her family eventually decided to terminate the pregnancy. After that, she followed a low-fat diet, and the condition improved quickly. TG fluctuated from 2.57 to 6.84 mmol/L, above the normal range in non-pregnant women (1.70-2.25 mmol/L).

The woman was pregnant again 11 months after the termination of her first pregnancy. In the first trimester, blood sugar and pressure were at a regular level, weight was 54Kg, and body mass index (BMI) was 21.6. The levels of TG went up and fluctuated from 2.65 to 20.29 mmol/L in the first trimester (12 weeks), so the pregnant women started with LMWH for managing the elevated levels of lipids, with LMWH 5000 IU, first IH, Qd from the 6th week of gestation,, and then IH, Bid when TG was at or above 11.3 mmol/L. Due to limited information on metformin's safety in fetuses, metformin was added from the 12th gestational week to regulate lipid metabolism (500mg, Po, Tid, taken within 30 minutes before meals). The level of TG was further up at about 16.15 to 47.65 mmol/L in the second and third trimester of pregnancy. Her first lipids test was taken in early pregnancy, and then regularly at 12, 16, 20, 24, 28, 32, 34, 37, and 38 weeks.

Admission Examination

The patient was admitted to the inpatient unit in the 38th week of gestation. The vital signs were typical, body temperature was 36.7 °C, blood pressure was 109/87 mmHg, and pulse and breath were 99 and 20 per minute, respectively. The fetal development was in line with gestational age. Ultrasound tips: low amniotic fluid, amniotic fluid index (AFI) was 78mm. The laboratory blood tests were as below (**Table 1**).

Table 1. Laboratory tests on hospital admission

	Results	Normal range of non-pregnancy
Triglyceride (TG)	40.9 mmol/L	Below 1.71 mmol/L
Blood pancreatic amylase	531.26u/ L	17.0-115.0u/L
D-dimer	1.00 ug/mL	Below0.5 ug/mL
White blood cell (WBC)	16.95 x 10^9/L	3.50-9.50 x10^9/L
Neutrophils (%)	81.5%	40.00-75.00%
Red Blood Cell (RBC)	4.08x10^9/L	3.80-5.10x10^9/L
Hemoglobin (HBG)	117 g/L	115-150 g/L
Platelet	148x10^9/L.	125-350x10^9/L

Admission diagnosis

The woman was diagnosed at admission with thirty-eight weeks of intrauterine pregnancy, left occipitoanterior (LOA), single live birth, hypertriglyceridemia. Considering that the patient had a history of HTGP that led to a pregnancy termination through induced labor, the relevant examinations and medical history were carefully completed after admission. The fetus had been full-term, and the patient did not exhibit a cephalopelvic disproportion. The

amniotic fluid volume was decreased, considering placental hypofunction. Labor was planned through vaginal trial production. An oxytocin challenge test (OCT) was performed to assess the reserve capacity of the fetus. After OCT became standard, misoprostol was administered to promote cervical ripening, and low-dose oxytocin was given for three days to induce labor. The woman had transvaginal delivery a live birth at 38^{+5} weeks, with a healthy weight of 2750g, Apgar scores at 1 minute were 8 and 5 minutes was 10.

Treatment management after delivery

The use of LMWH was stopped after labor and soon resumed 24 hours after delivery. The postpartum LMWH was given at 5000 IU, IH, Qd, while metformin was given at 500mg, Po, Tid, the doses were the same as that used during the pregnancy. The patient stayed at the hospital for seven days, and on the 10th day, LMWH discontinued after the D-dimer became completely normal.

The level of TG rapidly decreased at close to normal in a short time after delivery and continuing treatment management. Due to the placenta's delivery, the hormone secreted by the placenta could have a sharp drop in hypertriglyceridemia. The TG level was 20.11mmol/L on day three and further to 11.36 mmol/L on day 14, then the dose of metformin was changed to 500 mg, Po, Bid, taken 30 minutes before breakfast and dinner. Three weeks after delivery, when the TG level dropped to 5.03 mmol/L, the use of metformin was discontinued. On the 42^{nd} day after delivery, TG was at 2.03 mmol/L, close to the normal range. The infant was normal as those of the same age on the 28th day after birth. The child was one year and a half, with healthy development, according to the latest hospital visit.

DISCUSSION

In this case report, a pregnant woman who had developed hypertriglyceridemia-induced pancreatitis and terminated her first pregnancy through induced labor. In the second pregnancy, LMWH and metformin were used to manage hypertriglyceridemia and successfully avoided acute pancreatitis recurrence in pregnancy. This was a single case report on self-compared management.

The development of HTGP in pregnancy is closely related to a significant increase in TG levels but not serum cholesterol (12). A pregnant woman with TG above 11.3 or 22.6 mmol/L (e.g., 1000 or 2000 mg/L) in serum may have a very high risk of inducing acute pancreatitis (10, 13), after excluding gallstone- and alcohol-induced, which may account for 40-70% and 25-35% common causes of acute pancreatitis, respectively (14).

Diagnosis

The American College of Gastroenterology (14) recommends that the diagnosis of acute pancreatitis is most often established by the presence of two or three criteria: 1) Abdominal pain consistent with the disease, 2) Serum amylase and/or lipase 3-fold high of the upper limit of the normal range, and 3) Characteristic findings from abdominal imaging. In addition, contrast-enhanced computed tomography (CECT) and/or magnetic resonance imaging (MRI) of the pancreas should be reserved for individuals when a diagnosis is not precise or fails to improve clinically within 2-3 days hospital admission.

In Japan, the Research Group for Intractable Diseases and Refractory Pancreatic Diseases (15) also recommends similar criteria. However, they especially emphasize the etiology as important in determining acute pancreatitis, mainly, gallstone-induced and alcohol-induced acute pancreatitis, which may require different treatment.

Elevated levels of blood and urine amylase are essential for making a diagnosis of pancreatitis. About 90% of pregnant women with acute pancreatitis had elevated levels of amylase in blood and urine. Ultrasonic inspection is essential for diagnosing acute pancreatitis during pregnancy, and abdominal ultrasonic inspection may increase pancreatic volume, echo changes, and insubstantial structural inhomogeneity. In addition, the abdominal ultrasonic inspection is better than CT in its low radiation, because patients and their families are more likely to accept ultrasonic inspection. Therefore, patients with suspected pancreatitis should be given a priority of ultrasonic inspection of hepatobiliary pancreas and spleen.

Of note, due to the uterus enlargement gradually in the second and third trimester and deep anatomical position of the pancreas, abdominal pain in pregnancy with pancreatitis may be atypical, sometimes it might be misdiagnosed as threatened premature delivery, abortion, or placenta rupture. Therefore, attention needs to be paid when a pregnant woman is with abdominal pain, and the possibility of acute pancreatitis should be considered.

Treatment

While no established guidelines for managing HTGP in general, there have been some case reports of successful management using insulin, LMWH, and plasmapheresis (13, 16-19). The underlying mechanism is proposed that insulin increases the lipoprotein lipase activity, degrading the chylomicrons, to reduce serum triglyceride (16). Clinically, conservative treatments with fasting, anti-inflammatory, and infusion are often used to avoid miscarriage, premature delivery, and stillbirth. Because pregnancy caused hypertriglyceridemia, the conservative clinical treatment of HTGP may not be sufficient, although pregnancy can temporarily continue. However, the condition may develop rapidly, so serious complications such as acute necrotizing pancreatitis may occur and endanger the mother and fetus. Also, conservative treatments such as long-term fasting or poor eating may reduce maternal nutrition and affect fetal growth and development.

The termination of pregnancy in patients with HTGP has been a discussion in obstetrics and should consider the fetus's risk and the onset of pancreatitis. If a pregnant

woman has severe peritonitis or abnormal fetal heart rate and fetal distress, the pregnancy should be terminated actively. Alternatively, if a severe pancreatitis complication is related to pregnancy, continued pregnancy may aggravate the disease development and even endanger maternal life. Therefore, we are more willing to suggest terminating the pregnancy.

In this case report, a pregnant woman had terminated her last pregnancy in the second trimester when HTGP developed. However, active management of dyslipidemia during the second pregnancy, including closely monitoring the level of TG and preventive treatment with LMWH in the 6th week and metformin in the 12th week, leading to an improved outcome for both mother and fetus.

Possible mechanism of lipid-lowering

Lipid-lowering therapy is an essential treatment for HTGP. Insulin resistance may be one of the pathogenesis of dyslipidemia, and insulin treatment has been demonstrated effective in lowering the triglyceride in nondiabetic HTGP (18). As early as in the 1990s, studies have found that metformin affects lipid metabolism by inhibiting insulin resistance and achieves hypolipidemic effects in patients with non-insulin-dependent diabetes (20-22). In recent years, researchers have indicated that metformin may have an independent effect on reducing insulin resistance and lipids. The effect of metformin on reducing insulin resistance seems to appear ahead of lipid-lowering (23), suggesting a time-sequence manner in reducing insulin resistance and then lipid levels. Insulin plays a central role in lipid metabolism. As for how the insulin acts on the lipid metabolism, the mechanism is likely involved with multiple pathways (24-27), including the AMPK signaling and insulin-mediated activation of PI3K/AKT signaling.

Several studies have shown that LMWH reduces triglyceride and very-low-density lipoprotein (VLDL) while other lipoproteins are not affected, and complications such as bleeding are not increased (28, 29). Patients with hypertriglyceridemia often have a hypercoagulable state, and the incidence of thrombotic diseases increases during childbirth and puerperium. LMWH is effective in preventing thrombosis by improving lipid metabolism with minimal complications (30). In this case report, after treatment with LMWH, the patient had reduced the level of D-dimer within the physiological range of pregnant women.

So far, few studies have been carried out for an early drug intervention on hypertriglyceridemia in pregnancy. Pregnant women should have routine checks on blood lipid levels during pregnancy. Early detection of hypertriglyceridemia can help take early pharmacological intervention with metformin and LMWH to regulate lipid metabolism and prevent thrombosis. Diet control and preventive pharmacological treatment on hypertriglyceridemia may reduce the risk of developing HTGP in pregnancy. Although the report was on a successful case, the observation cannot be a formal recommendation for clinical practice. More patients should be examined for generating a hypothesis for a formal study.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the public-cation of this paper

ARTICLE INFORMATION

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