Report

Metformin Combined LMWH Intervention in 25 Pregnant Women with History of Hyperlipidemia Pancreatitis in Pregnancy

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ABSTRACT

Objective: To explore the early preventive treatment of hypertriglyceridemia-induced acute pancreatitis (HTGP) in pregnancy.

Methods: A retrospective cohort analysis was performed to examine the drug intervention on recurrent HTGP and related pregnancy outcomes among women who had HTGP in their past pregnancy and developed hyperlipidemia during the second pregnancy. Participants were identified through inpatient case records under a single physician at the clinic and divided into two groups. The intervention group was given metformin lipid-lowering combined with low-molecular-weight heparin to prevent thrombosis when hypertriglyceridemia was developed during the pregnancy. In contrast, the non-intervention group includes those who did not receive active drug treatment until they developed recurrent HTGP. Metabolic markers were also examined by comparing them with their respective past pregnancies.

Results: All participants experienced elevated triglycerides during their two consecutive pregnancies. No pregnant women developed HTGP in the intervention group (n=12), while 10 of 13 (76.9%) women developed HTGP in the non-intervention group. Thus, the outcome seemed to be markedly different. In the intervention group, 11 women were gestated to term, and one was premature; one of 12 (8.3%) births was neonatal asphyxia; there was no low-weight birth, and the prognosis of mother and baby was favorable. Of 10 women who developed recurrent HTGP in the non-intervention group, four suffered from fetal loss, four had premature, and two had full-term delivery; among the three pregnant women without HTGP, one had a premature and two had full-term births; five of thirteen (38.5%) births were neonatal asphyxia.

Conclusion: Pregnant women with HTGP history, if not treated, are likely to develop the condition recurrently during pregnancy, but timely intervention on hypertriglyceridemia with lipid-lowering and thrombosis-preventing seemed complete to reduce the recurrent HTGP and improve the pregnancy outcomes.

KEYWORDS

Metformin; low molecular weight heparin; triglyceride; pregnancy; hyperlipidemia; HTGP.

INTRODUCTION

Hypertriglyceridemia-induced pancreatitis (HTGP) in pregnancy is a particular type of acute pancreatitis with an incidence rate of about one per 25,000 births (1). When serum triglyceride (TG) levels reach 11.3 mmol/L or above, pregnant women are prone to develop severe acute pancreatitis. HTGP appears to be in the second and third trimester of gestations,

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characterized by acute onset, complications, and recurrent seizures (1, 2). The disease is dangerous. Maternal mortality and perinatal mortality could be as high as 20-50% (1, 3-5). While the etiology of HTGP is not clear, hypertriglyceridemia has become the second cause of acute pancreatitis in pregnancy(6). Large amounts of estrogen, progesterone and cortisol secreted in the body promote the production and storage of TG, total cholesterol, and plasma lipoproteins, which increase steadily with gestational week and reach a peak in the late stage of pregnancy (7). Hyperlipidemia increases the likelihood of developing HTGP, in which conservative treatments are less effective than other types of acute pancreatitis(2, 8, 9). Patients with severe HTGP often terminate a pregnancy once it occurs. However, when gestation is less than 28 weeks, the fetus survival rate is significantly lower. Therefore, clinical prevention of HTGP by treating hyperlipidemia is the key to ensuring that mothers and fetuses are safe and more clinically valuable than treating HTGP.

There are very few studies on whether pregnant women with hyperlipidemia should use drug intervention to prevent HTGP. To fill the gap, we performed a retrospective cohort analysis of two group women with a history of HTGP in their previous pregnancies. One group was treated for hyperlipidemia when it occurred; the other group did not treat it during pregnancy. Thus, timely intervention on hyperlipidemia seemed to benefits both mothers and fetuses.

DATA AND METHODS

Participants and diagnosis

Participants were pregnant women who developed HTGP and visited the physicians at our hospital clinic from 2006 to 2009. During that time, the investigator served as a chief resident and provided consultation on all HTGP in the hospital clinic. During this service, patients were informed to come back to the clinic when they got pregnant again. Some pregnant women revisited the outpatient clinic when they were pregnant and developed hyperlipidemia from January 2010 to January 2020. All participants were identified through the case records. The Ethics Committee of The Second Xiangya Hospital of Central South University approved this study; all patients provided informed consent.

HTGP diagnosis was made according to the diagnostic criteria of the China Guidelines for Diagnosis and Treatment of Acute Pancreatitis, serum TG concentration at 11.30 mmol/L and above, or serum TG 5.65-11.30 mmol/L, accompanied by chyle blood. Depending on the condition severity, diagnosis can be classified into 1) mild pancreatitis, which is not accompanied by organ dysfunction and local or systemic complications, 2) moderate pancreatitis, which is with past organ failure, 48h recovery, or with local or systemic complications, but no persistent organ failure, and 3) severe pancreatitis, which shows persistent organ dysfunction over 48 hours (1).

Drug intervention

All pregnant women in the intervention group followed a low-fat diet and standardized prenatal examination. From week 12, they were given metformin (500mg, po, tid), combined low molecular weight heparin (5000U, ih, qd). When patients are complicated with constipation, prebiotic Peifeikang was given at 210 mg, po bid, to regulate intestinal metabolism. When D-dimer levels reached more than 3-folds of their upper limits, the dose of low-molecular heparin was adjusted to 5000U, ih, bid. Those patients revisited the clinic in early pregnancy. Another group of patients with poor adherence did not come to the clinic until the onset of HTGP. While this design might cause selection bias, all patients were compared to examine the metabolic markers between current and past pregnancies complicated with HTGP.

Outcome and measurement

The primary outcome was the development of HGTP, and secondary outcomes included pregnancy outcomes and maternal lipid levels. The maximum lipid level was the highest value observed during pregnancy before and after treatment. Blood glucose and lipid levels were measured at fasting during the first prenatal examination of early pregnancy. BMI was measured and recorded before pregnancy and regularly reviewed later. Because cases were irregularly measured during clinic visits, only the maximum level was selected for each marker to monitor the dysregulation and interventional effect between two pregnancies. Lipid markers included TG, total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-CH), low-density lipoprotein cholesterol (LDL-CH), the ratio of HDL-CH to CHOL, lipoprotein a, LP(a), Lipoprotein A1 (APO-A1), Lipoprotein B (APO-B), D-dimer.

In addition, birth outcomes were also measured. These included gestational week, time of pregnancy termination, fetal weight, premature birth, birth weight, neonatal asphyxia, fetal loss, number of days in the hospital, and compared with their past pregnancies in each group. Finally, other related pregnancy outcomes and complications were extracted from the case recorded to compare the first and second pregnancies.

Statistical methods

SPSS 22 statistical package was used to process the data, the average of maximum levels of lipids was measured with Mean ± standard deviation (SD), blood lipid levels were compared between groups and within the group. While p-values were calculated for all outcomes within the group for self-comparison, they should not be used as hypothesis testing due to data limitations (10). In addition, a pairwise test was performed to compare blood lipid levels between two pregnancies with and without intervention.

RESULTS

Primary outcome

The study included 25 patients, 12 of whom were in intervention, and 13 were in non-intervention groups. Drug intervention affected the pregnancy outcome markedly.

Of 12 patients who received drug intervention, no complication of HTGP was observed. All pregnancies went well; 11 had full-term deliveries and one at 36 gestational weeks due to a premature rupture of the membrane caused by gestational diabetes mellitus. By contrast, in the non-intervention group, ten (77%) of 13 pregnant women developed HTGP, seven were severe, and three were moderate HTGP. They all met the diagnostic criteria for pregnancy complications with severe hyperlipidemic pancreatitis. After the disease onset during the second or third trimester of pregnancy, these patients were transferred to our hospital with abdominal pain, nausea, and vomiting in various degrees.

Lipid levels between pregnancies and intervention groups

Table 1 presents the lipid profile and D-dimer markers between two pregnancies in the intervention and non-intervention groups. The mean of TG, CHOL, HDL-CH, LDL-CH, APO-A1, and D-dimer were significantly lower in the intervention group ($P<0.05$), but no statistical difference in the mean of HDL-CH/CHOL, LP(a), and APO-B was found. By contrast, no significant difference in all lipid markers and D-dimer was found between the first and second pregnancies in the non-intervention group.

Table 1. Maximal levels of blood lipid levels and D-dimer between two consecutive pregnancies both in intervention and non-intervention groups

	First pregnancy		Second pregnancy			
	Mean	SD	Mean	SD	P	Normal range
Intervention group (n=12)						
TG	63.31	30.89	29.96	11.8	0.002	< 1.71mol/l
CHOL	24.21	8.06	14.67	5.01	<.001	2.90~5.20mol/l
HDL-CH	1.18	0.31	1.56	0.26	0.01	> 1.04mol/l
LDL-CH	12.33	3.31	7.27	4.63	0.04	< 3.12mol/l
HDL-CH/CHOL	0.10	0.04	0.12	0.05	0.224	0.15~1.00
LP(a)	229.98	159.5	167.61	53.83	0.23	0~300.0mg/l
APO-A1	1.19	0.25	1.75	0.21	<.001	1.00~1.60g/l
APO-B	1.16	0.58	0.76	0.36	0.081	0.10~0.77mol/l
D-Dimer	5.34	1.7	2.65	1.2	0.001	< 0.5ng/ml
Non-intervention group (n=13)						
TG	63.85	28.06	61.56	27.69	0.085	< 1.71mol/l
CHOL	22.84	6.7	24.38	8.53	0.081	2.90~5.20mol/l
HDL-CH	1.18	0.34	1.16	0.33	0.137	> 1.04mol/l
LDL-CH	11.77	3.99	11.78	3.64	0.966	< 3.12mol/l
HDL-CH/CHOL	0.13	0.12	0.12	0.12	0.808	0.15~1.00
LP(a)	253.02	209.7	221.6	163.3	0.1	0~300.0mg/l
APO-A1	1.19	0.24	1.22	0.28	0.528	1.00~1.60g/l
APO-B	1.18	0.69	1.17	0.63	0.956	0.10~0.77mol/l
D-Dimer	5.16	2.08	4.87	2.03	0.147	< 0.5ng/ml

Other related birth outcomes

Eight women had a vaginal delivery in the intervention group, and four had cesarean section due to scarred uterus (n=3) and arrested (n=1) labor during delivery. The mean gestational week was 38.58±1.20 weeks, the mean hospital stay was 4.33±1.61 days, and the mean birth weight was 3171.67±402.33 g, all of which were significantly different from their past pregnancy (**Table 2**).

In the non-intervention group, 10 (77%) pregnant women presented with a recurrent HTGP, with a mean pathogenic gestation of 28.04±6.29 weeks, the mean gestational week was 33.22± 4.97weeks, hospitalization of 18.08± 10.07 days, and newborn weight of 2340.77±954.07 g, all of which were not significantly different from that in their first pregnancies.

Table 2. General characteristics of pregnancy outcomes between the first and second pregnancy in the intervention (n=12) and non-intervention group (n=13)

	First pregnancy		Second pregnancy		
	Mean	SD	Mean	SD	P-value
Intervention group					
Age (year)	30.83	4.59	32.46	3.87	0.004
BMI (Kg/m$^{2)}$	22.79	2.63	20.73	1.60	0.02
Termination pregnancy (week)	34.02	3.87	38.58	1.20	0.002
Hospitalization days (day)	17.17	7.35	4.33	1.61	<.001
Newborn weight (g)	2147.5	802.17	3171.67	402.33	<.001
Non-intervention group					
Age (year)	30.46	3.99	32.69	3.79	<.001
BMI (Kg/m^2)	21.89	3.52	22.56	2.68	0.452
Pathogenic gestation (week)	28.64	5.91	28.04	6.29	0.646
Termination pregnancy (week)	32.45	4.23	33.22	4.97	0.316
Hospitalization days (day)	17.31	5.23	18.08	10.07	0.7
Newborn weight (g)	1962.31	557.2	2340.77	954.07	0.053

Four pregnant women who developed HTGP had a fetal loss. One severe patient was admitted when she was about to labor. The fetus presented with a weak heart rate and then died during delivery. One patient was subjected to induced labor during conservative treatment. Two patients with severe HTGP and gestational weeks less than 28 weeks received active symptomatic and supportive treatment, but not improved, so finally had induced labor.

Other six patients who developed HTGP actively received symptomatic and supportive treatment and improved. However, four had premature deliveries, and two had term births; five of six newborns had a low birth weight, and newborns and mothers exhibited noticeably poor prognoses.

Three patients who did not develop HTGP took an active low-fat and low-carbohydrate diet. They followed up with the Outpatient Clinic. Their TG levels ranged from 6.58 mmol/L to 38.56 mmol/L, and pregnancies went smoothly. Two women had term births and one premature birth with one neonate with low birth weight. The prognoses of the three mothers and their infants were satisfactory.

Other outcomes were also summarized in both intervention and non-intervention groups (**Table 3**) as it is seen that the interventional group seem improved in multiple other outcomes compared with their first pregnancy. However, no marked change was noted in the non-intervention group, although this was based on the limited sample size.

DISCUSSION

In this study of 25 cases, we found that preventing thrombosis and lowering lipid levels starting from the second trimester seemed to avoid HTGP effectively. This evidence was obtained by comparing with their respective past pregnancy. Patients with little drug intervention had a high chance of developing HTGP again, resulting in induced pregnancy termination. The drug intervention markedly improved lipid profiles and pregnancy outcomes. So far, studies related to drug intervention on hyperlipidemia in pregnant women have been rare. Free fatty acids degraded from TG by lipase might play a significant role in hyperlipidemia-induced pancreatitis. A rat model study has shown that free fatty acid lipid peroxidation might induce pancreatic acinar cell injury (11).

Pregnant women experienced a dramatic increase in hormones, particularly estrogen. The hormonal changes are required to enable the uterus and placenta to improve blood vessel formation and transfer nutrients for fetal development. However, the elevated hormones may initiate some pathological metabolic dysregulations in pregnancy (12). Patients with diabetes or gestational diabetes tend to have abnormal blood lipids from about 15 gestational weeks, primarily manifested by elevated TG levels. Therefore, with an aggravation of insulin resistance, abnormal glucose and lipid metabolism becomes increasingly severe (13). A case history analysis of patients with pancreatitis (n=577) and hypertriglyceridemia (n=272) showed that hypertriglyceridemia only accounted for 1.3-3.8% of acute pancreatitis in the general population. However, diabetes was present in 72%, hypertriglyceridemia, alcohol use, and gallstones were present in 77%, 23%, and 7% of patients, respectively, and lipase were elevated by two-fold as the upper limit of its normal range in 67% of patients (14). History of diabetes and hypertriglyceridemia appeared most common presentation in patients with acute pancreatitis.

Table 3. Complications, pathogenic gestation weeks, and fetal outcomes between the first and second pregnancy in the intervention (n=12) and non-intervention group(n=13)

	First pregnancy	Second pregnancy
Intervention group		
Cases with GDM or DM	5	5
Complications with biliary tract diseases	2	3
Pathogenic week of gestation	29.11±6.68	No disease
Neonates with a low-birthweight	6	0
Neonates with asphyxia	4	1
Premature births	6	1
Term births	1	11
Fetal losses	5	0
Non-intervention group		
Cases with GDM or DM	5	6
A complication with biliary tract diseases	3	3
Neonates with a low-birthweight	7	6
Neonates with asphyxia	5	5
Premature births	6	5
Term births	1	4
Fetal losses	6	4

GDM, gestational diabetes melliteus; DM, diabetes mellitus

Causes of pregnancy complicated with HTGP

Normal lipid metabolism during the pregnancy

After pregnancy, elevated estradiol, progesterone, and cortisol levels promote the formation and storage of fat and inhibit fat degradation and utilization. During the first two trimesters, pregnancy-caused hormonal and metabolic changes promote anabolism of lipids, during which the production and storage of TGs increase in preparation for the immediate energy need for the fetus in late pregnancy. Lipid synthesis is promoted by maternal hyperphagia and increased insulin resistance, which might be due to altered placental structure and functions associated with hormonal changes. Insulin resistance stimulates the fatty acid synthesis in adipocytes and lipoprotein lipase expression, which increases the uptake of circulating TG-rich lipoprotein.

The insulin resistance might involve a complicated etiology but may be associated with elevated levels of pregnancy-related hormones. Pregnancy-specific hormones include human chorionic gonadotropin (hCG), human placenta lactogen (hPL), human placental growth hormone (hPGH), of which hPL modifies maternal metabolic state to facilitate the energy supply of fetus and has anti-insulin properties and prolactin-like and growth-hormone-like activities. Prolactin, estrogen, and cortisol are elevated in maternal circulation during pregnancy, but no single hormone seems adequate to explain pregnancy insulin resistance (15).

However, during the third trimester of pregnancy, the "net" catabolism breaks down the lipids into smaller units such as fatty acids to release energy. The decrease in insulin resistance may increase the lipolysis of stored triglycerides in adipocytes, and the elevated levels of hPL also stimulate the lipolysis of stored TGs, which could lead to a decrease in the uptake of fatty acids from plasma TGs, and therefore, increase fatty acids and glucose in the circulation. Most of the mild and moderate elevation of lipids might be associated with pregnancy, but these may not necessarily induce pancreatitis. The imbalance between the catabolism and anabolism of lipoprotein may cause dyslipidemia in late gestation, which might have specific etiology beyond pregnancy.

Abnormal lipid metabolism and pancreatitis

A pathological lipid increase may occur when estrogen-induced TGs exceed a normal range during the middle and late pregnancy stages. Under such a condition, the increased TG functions as an initiator or promoter of acute pancreatitis (AP) (16). In addition, HTGP tends to occur in women with a history of abnormal lipid metabolism or associated with certain lipid metabolism disorders such as type III hyperlipoproteinemia with apolipoprotein E2 homozygotes (17, 18). In our study, all patients presented a history of pregnancy-induced dyslipidemia, and if not treated, dyslipidemia occurred again in the subsequent pregnancy and lead to HTGP. Thus, genetic predispositions might likely contribute to the etiology of pregnancy-complicated dyslipidemia (19).

Physiological hyperlipidemia due to pregnancy alone does not suffice to induce AP directly. Nevertheless, among people with underlying conditions such as obesity, the rapid growth of body mass, maternal age, diabetes,

preeclampsia, and other metabolic disorders, a physiological increase in blood lipids during pregnancy may be a high-risk factor for developing AP. While the underlying mechanism of HTGP is not precise, the pathogenesis of HTGP might be associated with that excessive TG hydrolyzed by activated pancreatic lipase and sudden inflammation due to something that triggers the digestive enzyme to activate inside the pancreas (20), which leads to massive accumulation of free fatty acids (FFA) in the pancreas. The elevated TG during pregnancy may result in embolism of pancreatic vessels due to condensed serum lipid particles. Highly concentrated pancreatic lipase breaks down serum triacylglycerol into glycerol and fatty acids, which may cause vascular micro-thrombosis and destroy the microvascular wall, resulting in ischemic necrosis of the pancreas followed by microcirculation disturbance. Elevated serum lipase has been associated with acute pancreatitis and has been used as a diagnostic marker for AP (21). In this study, the average age of 25 pregnant women was over 30 years, with the oldest of 40 years, 11 (44%) of abnormal blood glucose; the average body mass index (BMI) was above 20, and AP-related promoter in all patients.

Pregnancy associated cholelithiasis and gallbladder disease

A gallstone-related condition might account for more than 50% of pancreatitis in pregnancy (16) by alcohol-related diseases and hypertriglyceridemia. A high-fat and protein diet tends to stimulate gallbladder contraction and pancreatic hypersecretion in pregnant women. During pregnancy, under estrogen, the cholesterol concentration and progesterone level are elevated, bile duct smooth muscle becomes relaxed, and gallbladder motility is weakened, prolonging the time for gallbladder emptying. In pregnant women in the middle and late stages, the gallbladder volume increases by two times, but the bile excretion volume decreases, which increases the incidence rates of cholelithiasis and gallbladder diseases. For this reason, a high-fat and high–protein diet becomes a risk factor for pregnancy complicated with pancreatic diseases. Once necrotizing pancreatitis occurs, combined with hypertriglyceridemia and elevated fatty acid and cholesterol levels, the specific variations in hormone levels during pregnancy, hyperlipidemia, and AP will become more severe consequences. In the current study, five patients were complicated with biliary tract disease, which possibly increased the risk of HTGP.

Pregnancy with DM or GDM and blood lipids

Pathoglycemia is an inducing factor for pregnancy-complicated acute pancreatitis. Pregnancy-induced hormones such as human placental hormone have anti-insulin properties (22), which modify the maternal metabolic state to facilitate the fetus's energy supply. Insulin resistance has a profound impact on the metabolism of VLDL, a lipoprotein that carries cholesterol and TGs through blood (23). Therefore, glycemia is highly prevalent both in HTGP and dyslipidemia during preg-nancy (14). In addition, an observational study showed that gestational diabetes mellitus had been a long-term risk factor for pregnancy-related dyslipidemia defined by TG (24).

When the complication of hyperlipidemia occurs, serum amylase and lipase often present with false-negative testing. In the meantime, hyperlipidemia activates blood coagulation factors, resulting in platelet agglutination exhibiting a high-coagulation state as well as possible vascular damage (25). Under such a condition, one or more organs may occur within 72 h; therefore, it may cause pregnancy-complicated with AP to emerge earlier (26, 27). In the current study, 11 of 25 (44%, 5/12 in intervention and 6/13 in the non-intervention) patients had pathoglycemia; one DM patient complicated with severe HTGP presented with secondary superior mesenteric venous thrombosis, reversible posterior leukoencephalopathy, and secondary epilepsy.

Possible role of drug interventions in blood lipid reduction

The indirect effect of metformin on lipid-lowering

Metformin is the first-line medication for treating individuals with non-insulin-dependent diabetes mellitus (NIDMM) (28). It has shown improving glucose and lipid metabolism abnormalities in obese women drug-induced dyslipidemia (29-31), with relative safety and beneficial effect on weight and cardiovascular mortality compared with other drugs of its kind (32). In addition, metformin may have a potential advantage over insulin in treating gestational diabetes regarding maternal weight gain and birth outcome (33).

The molecular mechanism of action is not completely clear, but multiple potential mechanisms are likely involved. Metformin can inhibit liver glucose production through MAPK activation in hepatocytes by inhibiting mitochondrial respiratory chain complex I (34, 35), increasing insulin sensitivity, decreasing the insulin-suppression of the fatty acid metabolism, and glucose absorption from the gastrointestinal tract, and enhancing the peripheral uptake of glucose (28). The MAPK-independent effects of metformin on glucose production and lipid and cholesterol synthesis are likely through mitochondrial inhibition and counter-regulatory hormone glucagon (3, 36).

Insulin resistance is likely involved in dyslipidemia pathogeneses, as patients with primary hypertriglyceridemia present with noticeable insulin resistance (23). First, insulin resistance can result in excessive adipose tissue lipolysis, so the flux of free fatty acids (FFA) to the livers will increase, accelerating TG synthesis. Second, it is currently presumed that the high comorbidity of hyperinsulinism/insulin resistance in patients with hyperlipidemia is closely associated with hepatic insulin resistance (37-39). When insulin resistance occurs in the liver, the plasma FFA-suppressing effect of insulin decreases, leading to an increase in the plasma FFA concentration. Consequently, the amount of FFA entering the liver increases, and it will stimulate the liver to

synthesize and release very-low-density lipoprotein (VLDL) into circulation. In addition, hyperinsulinism/insulin resistance causes the decrease in the activity of lipoprotein lipase (40), a water-soluble enzyme that catalyzes the hydrolysis of the triacylglycerol part of circulating lipoproteins such as chylomicrons and VLDL into FFA and monoacylglycerol molecule (41), and thus increase the synthesis of TGs in the liver. Also, lipoprotein lipase has mediated the association of vitamin D with insulin resistance and type 2 diabetes (42).

Metformin decreases hepatic glycogen output by suppressing hepatic gluconeogenesis, which leads to the generation of glucose from fatty acids and proteins and improving insulin sensitivity by promoting insulin intake and utilizing insulin by peripheral insulin target tissues, skeletal muscle, and fat. Some *in-vitro* studies indicate that the binding between insulin and its receptor and the phosphorylation of the compound and tyrosinase activity can increase insulin sensitivity and suppress insulin resistance development (28, 43). In addition, metformin exerts its effect on lipid metabolism by suppressing insulin resistance to decrease the blood lipid level. A study has demonstrated that metformin reduces insulin resistance and lipid levels in a time-sequence manner in patients with antipsychotic-induced dyslipidemia (29). However, the mechanism remains unclear, and thus, needs to be explored in the future.

This study showed that metformin could decrease TC and TG in pregnancy-related dyslipidemia, but its effects on HDL-CH and LDL-CH were limited, likely due to the smaller sample size. Previously, metformin had been shown to decrease the postprandial TC and the concentrations of insulin and TG-rich enterogenous lipoproteins in patients with moderately or poorly controlled NIDDM (44). Therefore, we presume that for pregnant patients complicated with hyperlipidemia, particularly those with DM or GDM and obesity, metformin can reduce blood lipid and glucose to decrease the risk of pregnancy-related complications with HTGP.

Indirect HTGP-preventing effect of low molecular heparin

The episode of HTGP and elevation of TG are associated with the high-coagulation state of blood, which leads to insufficient blood perfusion into pancreatic tissue, thereby, may increase the risk of developing HTGP. Triglyceridemia may present a procoagulant state that involves blood coagulation and fibrinolysis disturbance, which is likely due to elevated plasma-activated factor VII and plasminogen activator inhibitor (45). Low molecular weight heparin (LMWH) can relieve the high-coagulation state of blood, decrease the TG level, and increase blood perfusion, thereby playing a vascular endothelial cell-protecting role. This function of LMWH maintains endothelial cells' normal function and structure, thus achieving an HTGP-preventing effect (46, 47).

Blood lipid-reducing effect of Peifeikang

Peifeikang combines *Bifidobacterium longum*, *Lactobacillus acidophilus,* and *Enterococcus faecalis* and is a viable triple capsule (48) probiotic supplement in China to treat pediatric antibiotic-associated diarrhea. In a rat model, Peifeikang was shown to decrease the production of proinflammatory tumor necrosis factor-alpha (TNF-α) and increased the anti-inflammatory cytokine interleukin 10 (49), likely through improving the dysbiosis of gut microbiota and metabolic phenotype of newborn rats (50).

In humans, probiotics might be effective for dyslipidemia. A meta-analysis of randomized clinical trials showed that probiotic supplementation could improve TC and TG concentration in patients with type 2 diabetes (51). However, other studies and reviews did not provide consistent evidence (52), which might be due to various factors such as the inclusion of study samples, type of probiotic supplement, and measurement of outcomes. Another study compared the treatment effect of metformin, probiotic supplement, and combination on lipid profile in patients with polycystic ovary syndrome (PCOS). It showed that all three medications significantly improved lipid profile after 12 weeks of treatment, and metformin combined with probiotics seemed to have additional beneficial effects on total cholesterol and HDL compared with either metformin or probiotics only (12). In addition, oral administration of Peifeikang can improve TC and LDL-CH levels in humans (53).

However, its mechanisms of action are not precise. Multiple studies show that a mixture of these three probiotics can reduce hepatic inflammation by improving insulin resistance and serum and liver TG concentration by inhibiting dietary absorption (54, 55). In addition, some *Lactobacillus* species have been proved to produce bile-salt hydrolase (BSH) (56), which reabsorbs bile acids via hepato-enteric circulation to promote the excretion of a large quantity of free bile acids from the intestines (57).

HTGP prevention and treatment: Present and future

Pregnancy complicated with hyperlipidemia is a high-risk factor inducing HTGP during pregnancy. Once it occurs, both mother and fetus may face a life-threatening condition. Conservative therapies, such as fasting, anti-inflammation, and fluid infusion, are frequently adopted in clinical practice to avoid pregnancy termination and premature delivery. However, specific pregnancy-related hormones aggravate hyperlipidemia, so HTGP may repeatedly occur even after conservative treatment. The condition may develop rapidly, with severe complications such as acute necrotizing pancreatitis, which eventually endangers maternal and fetal life. Therefore, often time, conservative treatment is eventually abandoned due to low efficacy. As a component of conservative treatment, long-term fasting or insufficient food intake may affect maternal nutrition and fetal development. Whether a pregnancy should be terminated for a pregnant woman with HTGP is a topic under discussion. Reasonably, a decision should be based on a comprehensive assessment of the fetal risk and whether the pancreatitis episode is related to pregnancy. If a pregnant woman presents with severe peritonitis or a fetus exhibits an abnormal heart

rate or distress, active termination of pregnancy should be sought. In addition, if severe pancreatitis in the patient is related to pregnancy and continued pregnancy may aggravate the disease or even threatens the maternal life, termination of pregnancy should also be performed.

Treatment of pregnancy complicated with HTGP is tricky, so prevention and early safe intervention should be actively conducted. Obstetricians should pay more attention to hyperlipidemia during pregnancy, particularly at the middle and late stages for those with a history of hyperlipidemia in pregnancy. Blood lipid and glucose should be regularly examined, and pregnant women are advised to avoid a high-fat diet. Hyperlipemia and hyperglycemia, metformin combined with LMWH seemed safe and effective based on our own experience whenever they occur. If necessary, multidisciplinary treatment can be provided. These strategies for patients with hyperlipidemia are expected to obtain satisfactory outcomes of pregnancy. Also, if women of reproductive age are found with hyperlipidemia at pre-pregnancy, intervention with metformin should be administered to regulate the blood lipid levels.

In addition, pregnant women with a healthy TG level before pregnancy should also monitor blood lipid levels. Diet regulation combined with drug intervention should be performed to control hypertriglyceridemia for those with a blood lipid level three times higher than the normal upper level. When the TG level exceeds 11.3 mmol/L, intervention with metformin is suggested for preventive treatment. Peifeikang can be used as an adjuvant intervention for pregnant women with constipation to improve gut microbiota, modulating metabolism, and reducing inflammation.

Pregnancy with HTGP is often complicated with a blood hypercoagulable state. When the D-dimeride level is three times higher than the normal upper limit, LMWH is recommended to reduce blood hypercoagulation. Patients with a history of HTGP have a noticeably higher chance of relapse, and once it occurs, pregnancy outcomes are often poor. Therefore, if a condition is detected early, education and management should be provided with a personalized treatment protocol, improving maternal and pregnancy outcomes and reducing mortality. Management and intervention are essential for patients with hyperlipidemia during pregnancy.

Limitations

Although this study is helpful and enlightening to a certain degree for clinical practice, its limited sample size and design may be biased. Diet and exercise reduce blood fat and glucose, impression that the benefit was derived from the drugs alone. In terms of future research, the potential benefit of a healthy diet should not be overlooked. A prospective study with an adequate sample size must formally evaluate drug intervention effectiveness and obtain evidence for clinical practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

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