Pancreatitis, pregestational diabetes and hyperchylomicronia in a pregnant woman with COVID-19

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Abstract

A 37-year-old pregnant woman, was diagnosed with acute pancreatitis whilst being infected with COVID-19. Additionally, she had a hyperchylomicronemia and an uncontrolled (most probably, pre-gestational) type 2 diabetes.

The coronavirus is able to enter the pancreatic cells through ACE-2 receptors. On the pancreatic level, ACE-2 receptor expression is present but not as abundant as on pulmonary level. However, with inflammation (due to hyperchylomicronemia), the ACE-2 receptor expression may change and hypothetically make the pancreas more susceptible for a Covid-19 surinfection.

Here it is difficult to conclude whether the COVID-19 infection contributed substantially to the development of pancreatitis. Late term pregnancy, uncontrolled glycaemia and the heterozygote mutation in the GPIHBP1 gene (c.523G>C p; Gly175Arg), all contribute to increased TG levels, a principal factor in the development of pancreatitis. This case shows a rare but serious clinical presentation late in pregnancy that could have interesting consequences postpartum. (Acta gastroenterol. belg., **2022,** 85, **637-639**).

Keywords: pancreatitis, COVID-19, pregestational diabetes, hyperchylomicronemia, GPIHBP1 gene.

Introduction

An acute pancreatitis in pregnancy is relatively common with an incidence of 1/1.000-10.000 pregnancies (1). The diagnosis is rarely made in the first and second trimester of pregnancy and it presents more frequently in multiparous patients (2). A pancreatitis originates mostly from migrating gallstones, alcohol abuse or viral infections. During the COVID-19 pandemic, several case reports (but not in pregnancy) have been published regarding the presence of an acute pancreatitis while COVID-19 positive. Indeed, previous rodent studies showed the development of a pancreatitis after inoculation with coronaviruses (3).

In a non-pregnant population, a severe hyper-TG (hypertriglyceridemia), is defined as a plasma triglyceride level >2000 mg/dl (according to the latest Endocrine Society guideline) (4). This lipid phenotype is associated with a significantly increased risk of pancreatitis (5). More specifically in this case, along pregnancy, a pronounced elevated TG level is found when VLDL synthesis is increased or the break-down of triglyceride particles (chylomicrons and VLDL) is reduced or a combination of both. After the second term of pregnancy, increasing estrogen levels upregulate VLDL synthesis, and together with a primary defect in LPL activity, this interaction (also known as the second-hit concept) could give rise to a pronounced hyper-TG and a subsequent pancreatitis.

Case Report

A 37-year-old woman, gestational age 25 weeks, presented to the emergency room with severe epigastric pain and fever. She had no respiratory distress, no diarrhea nor vomiting. She had no recent travel history and no other family members with similar symptoms. The patient reported no recent trauma, no alcohol nor drug use, no new medication or over the counter medication. She had normal vital signs except for a temperature of 38,1°C.

The patient's past obstetric history includes 5 term spontaneous vaginal deliveries (G8P5). 3 pregnancies were complicated by gestational diabetes. The patient did not return for a reevaluation of the glucose metabolism after her last pregnancy ("Zoet Zwanger project"). Nor did she had a follow-up in our endocrinology department or her family doctor. Her 12 year old son suffers from type 1 diabetes.

Physical examination shows epigastric tenderness. She appeared very uncomfortable, taking an antalgic position.

Her blood results are shown in table 1. A leukocytosis (7,1 x 1000/µL), elevated CRP levels (127,7 mg/L), normal liver enzymes, elevated lipase levels (157 U/L), normal kidney function, normal platelets 246 x 1000/µL, high blood glucose level (287 mg/dL) and an elevated HbA1c (9,4%). The triglycerides were significantly elevated (fasting: 1961 mg/dL) with an elevated, Apoliprotein B (1,57 g/L). Auto-immune screening (pancreatic antibodies, GAD65 antibodies, cardiolipine

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Submission date: 13/03/2021
Acceptance date: 03/08/2021

Table 1. — **Laboratory Findings**

Analysis	Reference values	Result
White blood cell count	4.0-10.0 x 1000/πL	7.1
Creatinine	0.50-0.90 mg/dL	0.20
eGFR	>90 mL/min	>90
Sodium	136-145 mmol/L	122
Potassium	3.5-5.1 mmol/L	3.9
Total bilirubin	<1.20 mg/dL	0.32
Direct bilirubin	<0.40 mg/dL	0.21
Transaminase GOT	<32 U/L	16
Transaminase GLT	<33 U/L	3
Gamma-GT	5-36 U/L	36
Alkaline fosfatase	35-104 U/L	70
LDH	135-214 U/L	222
Lipase	13-60 U/L	157
Glucose	70-100 mg/dL	255
Hemoglobin A1c	4.8-5.9%	9.4
CRP	<5 mg/L	127.7
Triglycerides	<150 mg/dL	1961

IgM and IgG) was negative. Urine analyses displayed a ketosis with a pH 5,0.

Due to her infectious clinical appearance, a naso-pharyngeal swab for COVID-19 virus (PCR) was taken and came back positive (with Ct-value of 25).

Imaging by MRI (as an ultrasound was not able to visualize the pancreas appropriately) shows an exudative pancreatitis (no necrosis) with fluid in the paracolic region (see Figure 1).

Therefore, our working diagnosis exists of an acute pancreatitis in the presence of a hyperchylomicronemia,

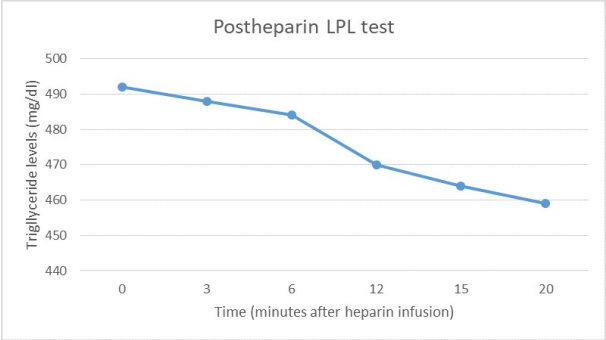

Figure 2. — Heparin lipoprotein lipase test.
A decrease in TG levels of 6,7% after 20 minutes.

a Covid-19 infection and an uncontrolled pregestational diabetes in the second term of pregnancy.

During hospitalization, supportive care was initiated using intravenous fluids, analgesics and insulin therapy. In order to lower the excessive TG levels, she starts fasting. With use of the TG-Apo B algorithm (hyper-Apo B: > 1,2 g/l, a hyper-TG:1961 mg/dl), we concluded that the origin of the hyper-TG was a mixed type. After giving birth, the hyper-TG persisted (1000 mg/dl).A post heparin lipoprotein lipase test (50 IU heparin per kg bodyweight, intravenously administered) gave a moderate TG decrease indicating a high probability for a disturbed lipolysis (figure 2). Genetic screening shows a heterozygote state of the c.523G>C p (Gly175Arg) mutation in the GPIHBP1 gene. In association with the lipid phenotype and disturbed lipolysis this variant is probably pathogenic (Class IV).

Discussion

Our patient who was in her second term of pregnancy presented with a combination of clinical features: an uncontrolled pregestational diabetes, an acute pancreatitis, a mixed pronounced hyper-TG with a mutation in

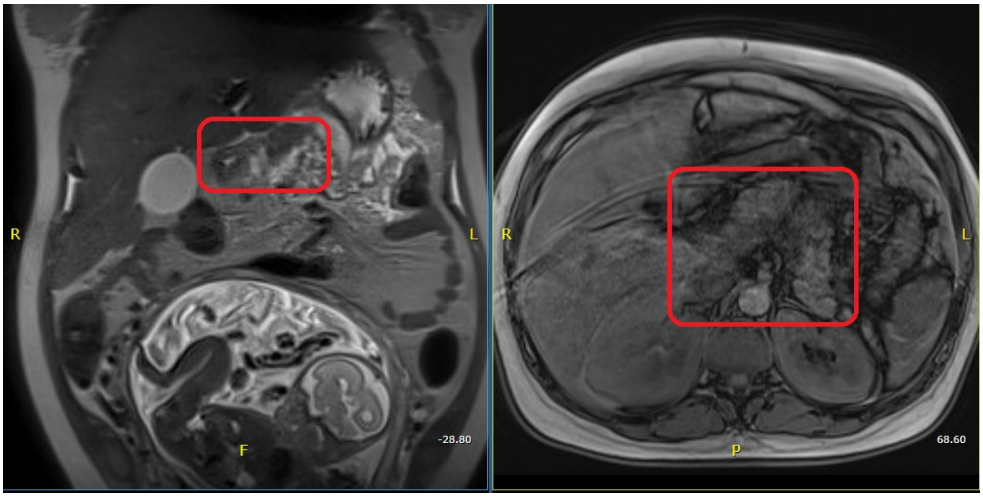

Figure 1. — MRI-imaging.
A frontal and tranversal view of the pregnant woman with pancreatitis.
The red outline indicates the pancreas.

the GPIHBP1 gene and an active Covid-19 infection. This combination is rather rare and gave rise to several clinical considerations.

Pancreatitis during pregnancy could be considered as a complicated disease for both mother and unborn child. Prior case reports mention a maternal mortality rate up to 37 % and a fetal mortality rate of 60 % (6). These percentages were lower in recent reports, with a mortality decrease to 0% and 3%, respectively, as a consequence of earlier diagnosis and improvement of maternal and neonatal intensive care treatment (1,2,7,8).

A mixed hyper-TG (both excess of VLDL and chylomicrons) is frequently found in the second term of pregnancy. The increase in VLDL synthesis results from both hepatic insulin resistance (uncontrolled pregestational diabetes) and the increasing estrogen levels along the duration of pregnancy. If, concomitantly, the LPL activity is defect, TGs will excessively accumulate in circulation with subsequently a toxic effect on the pancreas (9). After her pregnancy, her pronounced hyper-TG persisted, suggesting a primary limitation in the chylomicron clearance. Indeed, the post heparin LPL test shows a less than 10% decrease in TGs, suggesting a primary defect in LPL effectivity. A genetic screening revealed a heterozygote state of the c.523G>C p (Gly175Arg) mutation in the GPIHBP1 gene (OMIM 615947) and no mutation in LPL, Apo-E and Apo-C. GPIHBP1 is a protein that migrates LPL from the subendothelial space along the vascular endothelium towards the vascular luminal glycocalyx. The LPL is anchored to GPIHBP1 and the quality of this protein-protein complex determines its lipolytic action. Of interest, the heterozygous state of the GPIHBP1 gene mutation (in both humans and knockout rodent models) is mostly not primarily associated with a high lipid level, in contrast to the homozygous state (10,11). Therefore, another factor needs to be involved in the TG phenotype in our patient. In the pathophysiology of SARS-CoV-2, a generalized infiltration of the endothelium (vasculature) with viral elements is found with a subsequent pronounced local inflammation (12). Regarding the effect of a Covid-19 related endothelitis on LPL function to explain the hypertriglyceridemia in our case, is speculative. Another, more regular explanation, is the effect of an uncontrolled type 2 diabetes on the GPIHBP1-LPL binding complex and its final lipolytic activity (10,11).

Hypothetically, what may have been the potential role of the SARS-CoV infection in this case? Hitherto, its role in the evolution of a pancreatitis was not discussed before, especially not in pregnant women. As acknowledged, the virus enters the cell through the B-spike ACE-2 receptor. At the pancreatic level, ACE-2 receptor expression is present, but not as abundant as on the pulmonary level. However, in the presence of local inflammation (triggered by, for instance, excessive chylomicrons), the ACE-2 receptor expression may change and make the pancreas cell more prone to a Covid surinfection (13) (14). Nevertheless, due to the high counts in Covid PCR before it read off as positive, her Covid positivity may be considered as an "innocent" bystander. Currently it is not known whether immunity conversion (with a predominant change in T cell responsivity), as is physiologically found in the second part of pregnancy, may be of influence on the severity of Covid disease. In our patient, no progression towards a fulminant disease state (pancreatitis) was observed.

In conclusion, it is difficult to state against the background of current knowledge that the COVID-19 infection played a significant role in the development of her pancreatitis. Her significantly pronounced hyper-TG could be understood as a combined result of a heterozygous GPIHBP1 gene mutation, an uncontrolled (probably) pregestational type 2 diabetes and a pregnancy in progress. This combination could be in the origin of her pancreatitis. This total clinical picture is rare and not reported before.

Conflict of interest

There is no conflict of interest.

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