# Menstruation-Associated Acute Pancreatitis in Patients with Hereditary Pancreatitis

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Two adolescent girls presented with recurrent episodes of menstrual cycle–associated acute pancreatitis and are diagnosed with hereditary pancreatitis, a cause of chronic pancreatitis. Hereditary pancreatitis should remain in the differential diagnosis for teenage girls with catamenial acute pancreatitis and family history of pancreatic disease. *(J Pediatr 2021;230:248-50).*

Hereditary pancreatitis is one of the risk factors that leads to chronic pancreatitis and is characterized by early onset of disease, typically in childhood. Several genes have been associated with chronic pancreatitis including *PRSS1* (gene-encoding cationic trypsinogen), *SPINK1* (serine protease inhibitor, Kazal type 1), *CFTR* (cystic fibrosis), *CPA1* (carboxypeptidase A1), and *CTRC* (chymotrypsin C) genes, and other genes.[1-7] Hereditary pancreatitis classically has been described secondary to *PRSS1* genetic defects, most commonly a pathogenic *R122H* mutation (c.365G>A), has a variable spectrum of severity and presentation, and is clinically indistinguishable from other forms of acute pancreatitis and chronic pancreatitis.[8]

In a multinational cohort of 301 children with acute recurrent pancreatitis and chronic pancreatitis, 17% of individuals with acute recurrent pancreatitis and 46% of children with chronic pancreatitis had a pathogenic *PRSS1* mutation.[9] Approximately one-half of the patients with pathogenic *PRSS1* mutations progress to chronic pancreatitis by 20 years of age.[8,10] Few triggers are known to be associated with episodes of acute pancreatitis in patients with pathogenic *PRSS1* mutations, including alcohol consumption. One case report has previously shown onset of a menstrual cycle triggering episodes of acute pancreatitis in a teenage girl with Hereditary pancreatitis secondary to a pathogenic *R122H* mutation was reported.[11] A diagnosis of acute pancreatitis can be made according to subspecialty society recommendations, and specifically requires at least 2 of the following: abdominal pain compatible with acute pancreatitis, serum amylase and/or lipase values of 3 times upper limits of normal, or imaging findings consistent with acute pancreatitis.[12,13] We report 2 patients with hereditary pancreatitis and catamenial, defined as menstrual-cycle related, acute pancreatitis episodes.

## Case Reports

### Case 1

A 14-year-old girl with hereditary pancreatitis owing to a pathogenic *R122H* mutation (c.365G>A), and secondary pancreatic insufficiency, reports concordance of her period with bouts of acute pancreatitis. Patient had her first known episode of acute pancreatitis at the age of 13 years. Within 1 year, she has had 12 episodes of pancreatitis and 9 hospitalizations for acute pancreatitis at the Children's Hospital Colorado. The family and the patient report that the majority of her acute pancreatitis flares were catamenial. She had magnetic resonance cholangiopancreatography performed that did not reveal any evidence for pseudocyst or pancreatic necrosis. Her family history was significant for the patient's father having the same *PRSS1* mutation, but no bouts of pancreatitis, and a paternal aunt with the same genetic mutation and recurrent pancreatitis.

After consultation with adolescent medicine specialists, it was determined that hormonal menstrual regulation treatment had minimal harm or side effects and that the potential benefit was significant. The patient received continuous ovarian suppression with daily tablet containing 0.15 mg desogestrel and 30 $\mu$g ethinyl estradiol to decrease hormonal variations and attempt to decrease the frequency of the acute pancreatitis attacks. However, ovarian suppression, although well-tolerated and effective at halting her menstrual cycles, was ineffective at decreasing the incidence of episodes of acute pancreatitis. The patient progressed to a total pancreatectomy and islet autotransplantation 4 months after the initiation of hormonal regulation therapy.

### Case 2

A 16-year-old girl with a history of acute recurrent pancreatitis was found to have a heterozygous *R122H* mutation (c.365G>A) consistent with *PRSS1* and a variant of unknown clinical significance in *CFTR* (c.86A>T). At the time of initial presentation at the age of 15 years, the patient had epigastric abdominal pain and was admitted for acute pancreatitis. The evaluation included magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography,

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which revealed a prominent pancreatic duct with few dilated side branches and no evidence of pancreatic divisum. During the endoscopic retrograde cholangiopancreatography at Cincinnati Children's Hospital Medical Center, the patient underwent minor pancreatic sphincterotomy and placement of a prophylactic pancreatic duct stent with a single pigtail in the dorsal pancreatic duct. The family history was notable for her father having hereditary pancreatitis and local pancreatic surgery in his 20s, and for a sister who had undergone total pancreatectomy and islet autotransplantation, both secondary to *PRSS1*. The patient underwent genetic testing that revealed the same pathogenic variant.

She had attacks once per month at a time paralleling her menstrual cycle. These attacks were described as epigastric abdominal pain associated with nausea and vomiting lasting for approximately 6-7 days. Because the patient had no contraindications to hormonal suppression, she was started on a therapeutic trial of an oral daily tablet containing 0.15 mg desogestrel and 30 $\mu$g ethinyl estradiol. At 6 months of follow-up, the patient continued to report episodes of epigastric pain with or without the diagnosis of acute pancreatitis, despite suppression of her menses.

## Discussion

Herein, we present the cases of 2 adolescent females with the same *PRSS1* heterozygous mutation (*R122H*, c.365G>A) leading to hereditary pancreatitis who reported catamenial bouts of acute pancreatitis. Both patients had monthly recurrence of their menstrual pain and acute pancreatitis attacks pain, and 1 eventually progressed to total pancreatectomy and islet autotransplantation. As has been recommended, both patients were treated with ovarian hormonal suppression in an attempt to halt episodes of recurrent pancreatitis, but did not show resolution of episodes as anticipated.[14]

Heinig et al described a similar presentation of a 17-year-old girl with the same heterozygous mutation (*R122H*, c.365G>A) causing hereditary pancreatitis and recurrent bouts of catamenial acute pancreatitis.[12,14] This patient was initiated on ovarian hormonal suppression with continuous administration of a common pill used in Germany containing 0.03 mg ethinylestradiol and 2 mg dienogest. After menstrual periods ceased, only 1-2 further episodes of abdominal pain occurred, with lower lipase levels and the ability to avoid hospitalization. Furthermore, when this patient discontinued treatment, acute pancreatitis recurred with the onset of menstrual bleeding.[12]

Other reports indicate an association between atypical sites of endometriosis, including in the pancreas, which may lead to abdominal pain that can occur at the onset of menses; however, in these cases, cystic lesions of the pancreas or other laboratory abnormalities including an elevated white blood cell count and C-reactive protein have been reported.[15-17] Ectopic endometriosis was not assessed in the 2 patients presented here.

The pathophysiologic mechanisms by which hormones could trigger episodes of recurrent pancreatitis in patients with *PRSS1* mutations have not been reported. However, there are reports in animal models indicating that estrogen can affect the structure and function of the exocrine pancreas, leading to an increased risk of pancreatitis.[18,19] At the time of menses however, there is a decrease in the circulating levels of estrogen and progesterone. The association between hormonal variations in the menstrual cycle and acute pancreatitis attacks needs to be explored further.

Hereditary pancreatitis should be considered in the differential diagnosis for teenage girls presenting with cyclical abdominal pain concurrent with the onset of menses, especially when the family history includes family members with hereditary pancreatitis or pancreatic diseases. In these cases, catamenial episodes represent distinct bouts of acute pancreatitis and should be differentiated from other causes of recurrent abdominal pain such as irritable bowel syndrome, menstrual cramps, constipation, and other conditions. Although it has been suggested that in women whose symptoms and signs of pancreatitis recur in parallel with the menstrual cycle, hormonal ovarian suppression may be a safe and promising treatment strategy, our cases indicate that the pathophysiological association between hormonal shifts and recurrence of acute pancreatitis is complex.[12] ■

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