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A Pregnant Woman With Hypercalcemia-Induced Acute Pancreatitis

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INTRODUCTION

Hypercalcemia in pregnancy represents a challenge for the clinician. It is an uncommon condition with associated maternal and fetal complications. Diagnosing hypercalcemia is complex in pregnancy because symptoms are not specific and may mimic those in early pregnancy. Etiologic assessment and therapeutic management must also respect the fetal well-being.[1] *CYP24A1* loss of function leads to the overproduction of calcitriol, which can result in hypercalcemia. *CYP24A1* screening should be considered in non-parathyroid hormone (PTH) hypercalcemia during pregnancy; particularly as pregnancy may exacerbate hypercalcemia in mutation carriers.[2] We report the case of a pregnant woman who presented with recurrent pancreatitis which led to the diagnosis of hereditary hypercalcemia caused by a compound heterozygous mutation in the *CYP24A1* gene.

CASE PRESENTATION

Hypercalcemia (135 mg/l) was discovered in a 36-year-old gravida 3 parity 2 female patient at 14 weeks of gestation when she was hospitalized for pancreatitis which led to gallbladder removal surgery. Her medical history was significant for endometriosis, preeclampsia during her first pregnancy and gestational hypertension during the second pregnancy. She had already experienced abdominal pain with hypercalcemia the year before (Supplementary Table S1), without further complementary exams and with spontaneous improvement. She did not take any medication, including vitamin supplementation. Regarding her family history, her maternal grandmother was known to have hypercalcemia.

At admission, she presented with abdominal pain and nausea. Her vital signs were normal. Her laboratory findings were remarkable for elevated lipase levels, hypercalcemia, suppressed PTH levels, low PTHrp, normophosphatemia, hypercalciuria, and normal 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D levels. Angiotensin-converting enzyme level was normal. Kidney ultrasound showed bilateral medullary nephrocalcinosis without calculi (Figure 1).

We suspected chronic hypercalcemia and hypercalciuria, in regard to familial history, nephrocalcinosis and former episode of abdominal pain and hypercalcemia. The patient underwent genetic testing with

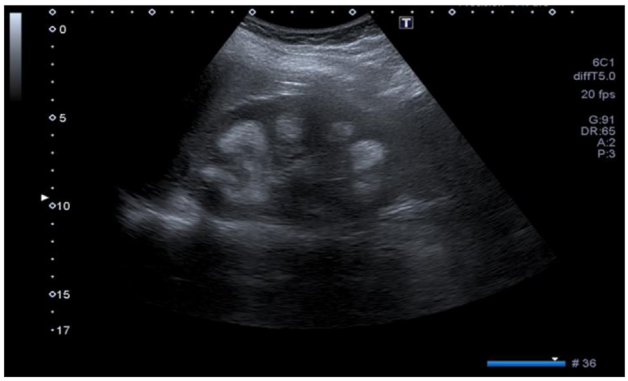

Figure 1. Ultrasound scan of the patient's right kidney showing diffuse echogenic pyramids suggestive of medullary nephrocalcinosis.

Table 1. Teaching points

- Hypercalcemia is a challenging diagnosis in pregnancy with potential deleterious consequences for the mother and the fetus.
- Hypercalcemia mediated by *CYP24A1* loss of function is probably underdiagnosed and its screening should be considered in non-PTH hypercalcemia during pregnancy.
- In hypercalcemia mediated by *CYP24A1* loss of function during pregnancy, the following simple measures can have great therapeutic effect: sunlight exposure avoidance, low-calcium diet, cessation of vitamin D supplementation.

targeted next generation sequencing, which confirmed a compound heterozygous mutation of *CYP24A1* gene: c.1186C>T,p.Arg396Trp; deletion of exons 9 to 11, respectively class 5 and 4 according to the American College of Medical Genetics and Genomics criteria,[3] therefore consistent with the diagnosis of hereditary hypercalcemia because of *CYP24A1* loss of function.

Our patient experienced 3 recurrent episodes of hypercalcemia-associated acute pancreatitis during pregnancy, resolving with hydration and sunlight exposure avoidance. She presented no adverse peripartum outcomes and delivered a 3.8 kg girl. Both mother and daughter had normal calcemia levels after delivery.

DISCUSSION

CYP24A1 gene encodes a vitamin D 24-hydroxylase mitochondrial enzyme which catalyzes the degradation of the active form of vitamin D, 1,25-dihydroxy vitamin D (calcitriol), into the multistep 24-oxydation pathway to calcitroic acid.[4] *CYP24A1* gene mutations are inherited in an autosomal recessive pattern; *CYP24A1* loss of function leads to the overproduction of calcitriol which can result in hypercalcemia, hypercalciuria, and low PTH. Phenotypes can be variable, from asymptomatic or milder form diagnosed at adulthood to severe forms diagnosed early during infancy.[5,6] Vitamin D supplements prescribed during pregnancy can aggravate hypercalcemia. Pregnancy and lactation may also exacerbate hypercalcemia in this disease, as a result of increased calcitriol because of increased production of renal and placental 1-α hydroxylases in response to estradiol, placental lactogen, and prolactin.[7,8] These phenotypes are usually associated with calcitriol levels in the upper normal range. An increased 25-hydroxy vitamin D to 24,25-dihydroxy vitamin D concentration ratio seems to be associated to *CYP24A1* loss of function.[7]

Hypercalcemia diagnosis is challenging in pregnancy because symptoms such as asthenia or nausea can mimic those in early pregnancy. Hypercalcemia can lead to maternal complications (nephrolithiasis, pancreatitis, preeclampsia, hypertension, and depression), growth restriction of the fetus, and severe neonatal hypocalcemia because of fetal hypoparathyroidism (usually transient lasting a few months after birth).[1] Main etiologies of hypercalcemia in pregnancy are summarized in Supplementary Table S2. After ruling out the most frequent causes (hyperparathyroidism, iatrogenic, granulomatosis, and malignancy), genetic testing appears as an interesting tool regarding its safety and the easier access to genetic platforms.

Considering the mechanisms involved in *CYP24A1* loss of function, hydration is crucial and must be associated with the following simple measures that can have great therapeutic effect: sunlight exposure avoidance, low-calcium diet, cessation of vitamin D supplementation. Use of bisphosphonates or azole agents is currently not recommended for hypercalcemia in pregnancy. Use of steroids is not recommended in *CYP24A1* mutations because their therapeutic benefit requires a functioning vitamin D 24-hydroxylase enzyme.[9] Calcitonin has been used in pregnancy in this condition[6] but with a risk of tachyphylaxis and limited data regarding its safety in pregnancy.

In conclusion, this case highlights the importance of genetic screening in non-PTH related hypercalcemia in pregnancy and describes the specificity of pathophysiology, outcomes, and treatment in *CYP24A1* mutations during pregnancy (Table 1).

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in the report.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Laboratory findings.

Table S2. Main etiologies of hypercalcemia in pregnancy.

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