CASE REPORT

1. Resident Physician of Gynecology and Obstetrics, Universidad Libre Cali, Colombia
2. Specialist in Maternal Fetal Medicine, National Institute of Perinatology, Colombia.

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Correspondencia:
Luisa Fernanda Cano Bautista
Cdra. 86 25-83, Cali, Colombia. Código Postal: 760026
(+57) 3232089363
luica14@hotmail.com

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Hypercalcemia in pregnancy
Hipercalcemia en el embarazo

Luisa Fernanda Cano Bautista[1], María Alejandra Aguirre Martínez[1], Jorge Ricardo Paredes[2]

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ABSTRACT
Hyperparathyroidism during pregnancy is not a frequent diagnosis and is generally a diagnosis of exclusion. It may present with emetic episodes, alteration of the mental sphere and of the state of consciousness, and abdominal pain. This causes difficulties in its initial diagnosis and delay in starting treatment that leads to complications such as gestational loss. The case presented is of a 30-year-old pregnant woman of 8.5 weeks, with no known history of chronic hypertension, who was admitted with neurological symptoms associated with persistent hyperemesis, polyarthralgia and hypertensive crisis. Autoimmune disease was ruled out. She had normal vitamin levels, with evidence of altered renal function, hypercalcemia and calciuria, renal ultrasound with nephrocalcinosis and thyroid ultrasound with apparent parathyroid mass. She showed a torpid neurological evolution. The diagnosis was primary hyperparathyroidism with high obstetric risk, requiring termination of pregnancy and resection of the parathyroid lesion. Symptomatology, renal function and calcium levels improved. Primary hyperparathyroidism is not a frequent etiology in pregnant women, being more a diagnosis of exclusion, with a wide spectrum in its clinical presentation.
Key words: Hyperparathyroidism, Hypertension, Hypercalcemia, Pregnancy complications

RESUMEN
El hiperparatiroidismo durante la gestación no es un diagnóstico frecuente y generalmente es de exclusión, pudiendo cursar con episodios eméticos, alteración de la esfera mental y del estado de conciencia y dolor abdominal. Ello genera dificultades en su diagnóstico inicial y demora para iniciar el tratamiento, pudiendo aparecer complicaciones como la pérdida gestacional. El caso que se presenta es de una gestante de 30 años con embarazo de 8,5 semanas, antecedente no conocido de hipertensión crónica, quien ingresó con sintomatología neurológica asociada a hiperémesis persistente, poliartralgias y crisis hipertensiva. Se descartó enfermedad autoinmune. Tenía niveles de vitaminas normales, pero con evidencia de función renal alterada, hipercalcemia y calciuria, ecografía renal con nefrocalcinosis y ecografía de tiroides con aparente masa paratiroidea. Mostró evolución neurológica tórpida. El diagnóstico fue hiperparatiroidismo primario con alto riesgo obstétrico, requiriéndose la finalización de la gestación y resección de la lesión paratiroidea. Ello mejoró la sintomatología, la función renal y los niveles de calcio. El hiperparatiroidismo primario no es una etiología frecuente en las gestantes, siendo más un diagnóstico de exclusión, con un amplio espectro en su presentación clínica.
Palabras clave. Hiperparatiroidismo, Hipertensión, Hipercalcemia, Complicaciones del embarazo

Introducción

Primary hyperparathyroidism is a typical disease in middle-aged and elderly women[1]. It is considered the third most common endocrinological disorder in the general population with a prevalence of 0.1-0.4%[2]. It is a rare disease during gestation, with no exact incidence due to the poor association between the symptoms presented. Some authors find an incidence of about 0.05%[3].

Eighty percent of pregnant women with primary hyperparathyroidism may be asymptomatic and be identified during routine laboratory studies. Therefore, it is important to inquire during the consultation about symptoms of hypercalcemia that could be masked by the physiological changes of pregnancy[4]. Among the recognized symptoms are lethargy, decay, nausea, vomiting, polyuria and polydipsia, as well as constipation, abdominal or epigastric pain, depression, confusion, which may occur in up to 20% of cases[5].

Some women may present with hyperemesis gravidarum, acute pancreatitis, nephrolithiasis, preeclampsia and hypercalcemic crises when appropriate management is not established, as well as alterations in fetal health such as neonatal tetany, hypoparathyroidism, growth restriction, preterm delivery, miscarriage or intrauterine death[4,5].

Diagnosis is based mainly on clinical suspicion, since during gestation and due to physiological changes, the interpretation of levels due to hemodilution, increased glomerular filtration rate and hypoalbuminemia represent a challenge in this period. Additionally, calcium is not a routinely requested electrolyte[3].

There is no consensus on the management of hyperparathyroidism during pregnancy. Individualized management is required according to the requirements of each patient and according to the clinical presentation, considering that patients with serum calcium concentrations lower than 2.85 mmol/L (11.42 mg/dL) should be managed conservatively[4]. Medical management includes hydration, calcium supplementation (calcitonin, calcimimetics) and lithium, if possible. However, surgery remains the only curative option for this pathology[4,6].

Case presentation

A 30-year-old black female patient, in her third gestation, with a viable pregnancy of 8.5 weeks by ultrasound and a history of unmanaged chronic arterial hypertension, reported a one-week history of episodes of severe headache associated with insomnia, myalgia and generalized arthralgias that limited gait.

She was admitted to the emergency department with blood pressure in crisis range, without relevant findings on physical examination, preserved osteotendinous reflexes, without pain on muscle palpation of the lower or upper limbs or inflammatory signs. There was no alteration in sensitivity, but bradypsychia and somnolence. Laboratory tests were requested, showing alteration in renal function due to elevated serum creatinine, hemogram with leukocytosis and thrombocytosis without anemia, elevated C-reactive protein. Given the possibility of autoimmune disease associated with polyarthralgia, an immunological profile was performed, which was negative. During surveillance, the patient presented fluctuation of consciousness between somnolence and episodes of hyperactivity, with auditory hallucinations and aggressiveness, in addition to adynamia and decreased strength in lower and upper limbs, requiring support for movement.

Due to the persistent hyperemesis, Wernicke-Korsakoff syndrome was not ruled out, vitamin B1 levels were requested and vitamin B1 supplementation was started. The studies were complemented with vitamin B12, ferrokinetic profile, liver function and creatine phosphokinase, which were found to be within normal limits. Due to deterioration of renal function, renal ultrasound was performed, which described nephrocalcinosis, with a report of positive 24-hour calciuria (452 mg/dL) and serum calcium levels outside the target range (19.4 mg/dL), which could be due to glomerulonephritis and/or renal damage secondary to chronic hypertension. However, hypercalcemia was noteworthy.

Parathyroid hormone was found in alert range due to its marked elevation (454 pg/mL). Thyroid ultrasound identified a solid heterogeneous lesion in the left lower lobe measuring 30 x 22 mm, and it was not ruled out that it was related to the parathyroid. The patient persisted in her disorientation over time, asthenic and adynamic, with incoherent language and episodes of confusion. Pending brain MRI, severe hypercalcemia required monitoring in the intensive care unit. Management with diuretics, bisphosphonates and steroids was initiated.

Given the high risk of maternal morbidity and mortality, and in consensus with the patient, gestation was terminated at 10.3 weeks. After management, the patient presented resolution of hypercalcemia with improvement and stability of renal function without requiring dialysis, and with resolution of mental alterations.

Discussion

Calcium metabolism disorders in adults are related to parathyroid hormone secretion, as evidenced by primary hyperparathyroidism or chronic hypoparathyroidism[7]. However, primary hyperparathyroidism is the most common endocrinological disorder, especially in women, which is most often diagnosed in the reproductive age[7].

During gestation, hyperparathyroidism is considered a rare disease with a prevalence of 0.05%, the main cause being hypercalcemia which generates high maternal and neonatal morbimortality[8]. In most cases, hyperparathyroidism during gestation is of the primary type, with the presence of parathyroid adenomas in 85%-89%[8]. Other causes include multiple adenomas of the gland or hyperplasia in 9% and parathyroid cancer in 2%[9].

Physiologically, changes in calcium homeostasis during gestation are due to calciotropic hormones, which may mask primary hyperparathyroidism[10]. During this stage, total calcium levels decrease, which is associated with the hypoalbuminemic state. However, the levels of ionized calcium, i.e., the physiologically active fraction, remain unchanged. On the other hand, the increase in glomerular filtration rate results in hypercalciuria.

A total of 25-30 g of activated calcium is transported from the mother to the fetus through the placenta to promote fetal bone formation and growth. This transport is independent of maternal parathyroid hormone levels and is mediated by the secretion of placental parathyroid hormone-related protein[10]. This calcium homeostasis allows preservation of maternal bone structure. Excess parathyroid hormone acts on bone with increased osteoclastic function, causing an increase in serum calcium. In turn, the kidney increases the elimination of phosphorus and the reabsorption of calcium. Activated vitamin D is also increased, which accentuates calcium reabsorption at the intestinal level[11].

Excessive passage of calcium to the fetus causes suppression of fetal parathyroid hormone and increased calcitonin which, if not corrected early, causes high fetal morbidity and mortality, neonatal tetany and seizures[11]. Other fetal complications include growth retardation, preterm delivery, miscarriage and neonatal death.

The diagnosis of primary hyperparathyroidism in pregnancy is usually delayed, as only 20% of patients tend to present symptoms and some of them simulate other common conditions such as the presence of nausea and vomiting. A high index of suspicion to detect hyperparathyroidism in a pregnant woman is the presence of conditions such as nephrolithiasis, pancreatitis, peptic ulcer, bone fractures or the atypical presentation of hypertensive disorders[9], as occurred in our patient.

On the other hand, psychotic symptoms have been detected in patients with hypercalcemia, with variable severity depending on circulating calcium levels, in addition to the hypertensive disorder. The exact mechanism by which primary hyperparathyroidism causes psychotic symptoms is unclear. However, the role of calcium in modulating dopaminergic and cholinergic metabolism, as observed in patients with schizophrenia during catatonic episodes, has been identified[12]. This behavior was present in the patient with auditory and visual hallucinations.

Primary hyperparathyroidism is characterized by elevation of serum ionized calcium or albumin-adjusted calcium, with elevation of parathyroid hormone. During gestation, parathyroid hormone levels physiologically decrease due to elevation of hormone-related protein around 3-13 weeks of gestation with a peak in the third trimester, leading to parathyroid hormone suppression. For this reason, parathyroid hormone levels may be lower than expected. And, if hypercalcemia is found in the presence of unsuppressed parathyroid hormone, primary hyperparathyroidism during gestation is suspected[4].

Among the laboratory tests necessary for diagnosis are ionized calcium, albumin-adjusted calcium, intact parathyroid hormone, phosphorus, magnesium, free T4, free T3, complete blood count, alkaline phosphatase, calciuria and creatinuria in 24 hours and creatinine clearance[4]. Diagnostic imaging during pregnancy has a sensitivity of 76%-87% for the identification of abnormal parathyroid tissue, with a specificity of 94%-96%, so it is only considered to be requested in patients who are going to undergo surgery[4].

Regarding treatment, there is still no consensus on the management of primary hyperparathyroidism during pregnancy. Therefore, individualized management should be performed for each patient according to the severity of symptoms, the gestational age of presentation, the age of the patient and the presence of complications. Conservative treatment options include[13]:

- Oral phosphates: category C during pregnancy; they are generally well tolerated. Side effects include hypokalemia and diarrhea, in addition to multiple organ failure due to extravascular calcium phosphate deposits.

- Furosemide: category C, promotes calciuresis by blocking renal tubular reabsorption of calcium.

- Calcitonin: category B, decreases serum calcium levels by direct inhibition of osteoclastic function.

- Cinacalcet: category C, is a calcimimetic that activates the receptor that sensitizes calcium present in parathyroid cells, thyroid c-cells and renal tubular cells, reducing renal reabsorption of calcium independent of parathyroid hormone changes.

- Bisphosphonates: category C due to their transplacental passage; they should be used in emergencies as a short-term intervention to stabilize severe hypercalcemia before surgery.

In those patients in whom definitive management is defined, parathyroidectomy is the appropriate management. This should be performed in the absence of control of serum calcium levels or the presence of severe symptoms at older gestational age. The appropriate time for intervention is the second trimester due to the low risk of preterm delivery induced by anesthesia and the lower teratogenicity due to complete organogenesis[13].

In conclusion, primary hyperparathyroidism during gestation is a diagnostic challenge due to the masking of the pathology by other common conditions such as hyperemesis gravidarum. So it is of vital importance its clinical suspicion through laboratory tests in order to institute early management.

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