Hiperparatireoidismo primário na gravidez tratado com bisfosfonatos

Primary hyperparathyroidism in pregnancy treated with bisphosphonates

Patrícia Tavares, Gustavo Rocha, Catarina Machado, Maria João Oliveira

Portugal. Servicio de Endocrinología. Centro Hospitalar Vila Nova de Gaia/Espinho

Introduction

The diagnosis of primary hyperparathyroidism (PHPT) is made when hypercalcemia and elevated parathormone (PTH) levels are present and most of cases are due to single parathyroid adenomas[1].

It is the third most common endocrine disorder after diabetes mellitus and thyroid disease, but is much less common during pregnancy[2,3].

PHPT mainly affects women in older age groups, with only 5–10% of cases diagnosed in women of reproductive age. In the general population, the prevalence is about 0.1-0.4% but in pregnant women the precise incidence is unknown[4].

Maternal and fetal complications of moderate/severe PHPT during pregnancy are recognized (around 67% and 89% respectively) but the diagnosis may be missed, misleading or masked by physiological changes and overlapping clinical symptoms associated to this period of life[1].

Recent studies show that PHPT during pregnancy with serum calcium levels only mildly elevated is generally not associated with an increased risk of obstetrical and fetal complications[2,3]. It is now recognized that PHPT has a large spectrum presentation and it is highly expected that severe symptomatic disease has different maternal and fetal effects compared with mild disease[3]. For that reason, the distinction between mild disease, which may be observed, and the clinically significant one, which should be treated, is crucial.

The surgical treatment is recommended mostly in second trimester [1] but there are no guidelines indicating the exact medical treatment when the surgical approach is not possible.

We describe a case of PHPT during pregnancy treated with furosemide and pamidronate.

Palabras clave: Hipercalcemia. Embarazo. Bifosfonatos. Pamidronato. Hiperparatiroidismo primario.

Keywords: Hypercalcemia. Pregnancy. Bisphosphonates. Pamidronate. Primary hyperparathyroidism

Case presentation

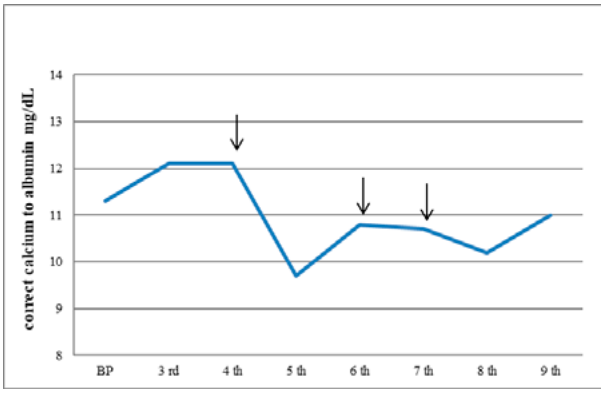
A 31-year-old Caucasian woman with a history of renal lithiasis since she was 18 years old was referred to an endocrine consultation. She presented with high PTH 171.4 pg/mL (15.0-65.0), hypercalcemia 11.3 mg/dL (8.8-10.2), hypophosphatemia 1.9 mg/dL (2.7-4.5) and normal vitamin D levels. The cervical ultrasound did not show parathyroid localization.

Bone densitometry and Tc99m-sestamibi scintigraphy were requested. Unexpectedly the patient did not perform these exams because she had unintentionally become pregnant (gestation of 12 weeks). A diet with calcium restriction and strict oral hydration was instituted but, despite that, the patient experienced worsening of nausea and vomiting, with marked hypercalcemia (correct calcium to albumin 12.1 mg/dL). She started furosemide 20 mg/day at 15 weeks of gestation to a maximum dose of 120 mg/day.

A cervical ultrasound was repeated but, for the second time, no parathyroid gland was identified. Exploratory surgery was proposed in her second trimester of pregnancy, but she refused and postponed it to the postpartum period. Options for medical management were therefore explored.

Despite the measures described above, serum calcium levels remained elevated and symptoms became worse. Treatment with a bisphosphonate was decided and the patient underwent the first treatment with pamidronate 60 mg IV at 21 weeks of gestation. At that time the calculated calcium for albumin was 12.3 mg/dL. After the first infusion of pamidronate, there was a subsequent decline of the calcium concentration levels. However, due to clinical and analytical exacerbation, she repeated pamidronate infusion at 25 and 30 weeks of gestation, with a decline of serum calcium between doses (Fig 1).

Figure 1. Calcium levels during pregnancy, arrows – pamidronate treatments



Legend: arrows: pamidronate treatments; BP: before pregnancy, numbers: Pregnancy month

Prior to the administration of the drug the side effects in the short term and the lack of knowledge of long-term side effects were explained to the patient and she signed a written consent to this therapy.

Fetal ultrasound examination was normal, and biometry showed normal fetal development.

Correspondencia: patriciatavares.med@gmail.com

Cómo citar este artículo: Tavares P, Rocha G, Machado C, João Oliveira M
Hiperparatireoidismo primário na gravidez tratado com bisfosfonatos. Galicia Clin 2019; 80 (2): 22-23

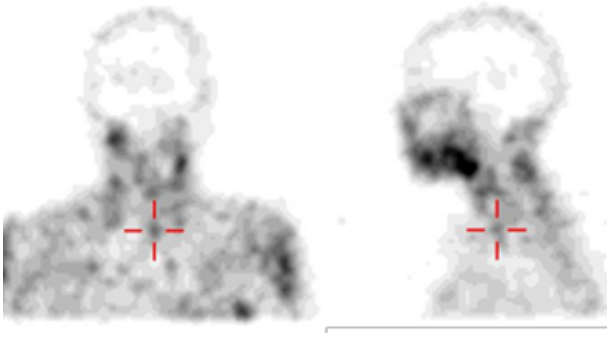
Recibido: 25/03/2018; Aceptado: 29/05/2018 // http://doi.org/10.22546/52/1649

The delivery was anticipated due to clinical manifestations, mainly the persistent nausea and vomiting. An elective caesarean delivery was performed at 37 weeks of gestation without complications. A female of 2800g was born, with Apgar 9/10 and no episodes of hypocalcemia in the neonatal period.

The sestamibi scintigraphy performed in postpartum period showed a hyperfixation focus inferiorly to the left lobe of the thyroid gland (Fig 2). The patient was submitted to a left inferior radioguided parathyroidectomy with intraoperative PTH evaluation that enabled the correct identification and removal of the enlarged gland with consequent normalization of PTH and hypercalcemia. The pathological exam confirmed a 15x5 mm parathyroid adenoma.

The child, now a two years old girl, is healthy, and has normal motor, cognitive and psychosocial development.

Figure 2. Sestamibi scintigraphy



Discussion

Maternal-fetal complications

In the final weeks of gestation, the foetus needs 25 to 30 g of calcium for bone mineralization[5]. In order to meet those fetal needs, intestinal calcium absorption doubles under mediation by calcitriol, prolactin, and placental lactogen [6]. This calcium is actively transported across the placenta resulting in suppression of fetal PTH secretion until after delivery. In maternal PHPT, this gradient is further elevated, resulting in a state of fetal PTH suppression and in a potential hypocalcaemic state and tetany in the new-born due to parathyroid hypoplasia [7].

Additional neonatal complications include neonatal hypoparathyroidism (manifested in only 12% of neonates), mental retardation and low birth weight[2].

Reported maternal complications include hyperemesis, nephrolithiasis, muscular weakness, mental symptoms, skeletal pain, fatigue, pre-eclampsia, pancreatitis and hypercalcaemic crisis (reported for calcium levels >14 mg/dL)[2,5].

It is reported that about 48% of pregnant women with untreated PHPT suffer miscarriages. Most of these cases occurred in the late first trimester or early second trimester and were related to the serum calcium levels. Miscarriage is more common as calcium levels exceed 11.4 mg/dl. Normal et al reported that 72% of all pregnancy losses occurred in women with serum calcium levels of 11.4 mg/dl or higher. Once the mean serum calcium levels exceed 12 mg/dl, a full term pregnancy is even more unlikely[8].

Even though many pregnant women with PHPT reach a state of normocalcemia (explained by the specific physiology of pregnancy such as hemodilution, hypoalbuminemia and maternal hypercalciuria), our patient presented with a progressive increase in the calcium levels, with a maximum of 12.3 mg/dL despite the initial measures of hydration reinforcement and forced diuresis.

In addition to the risk of spontaneous abortion, pancreatitis and pre-eclampsia may also occur, even with lower calcium levels compared to those of our patient[9].

Even with calcium levels superior to those associated with adverse maternal and fetal outcomes, treatment prevented further calcium elevations, therefore minimizing the risk of these complications.

Location techniques

Sestamibi scintigraphy, the usual technique used for detecting parathyroid adenomas or diffuse parathyroid hyperplasia, is not recommended in pregnancy due to the risk of ionizing radiation for the foetus. Neck ultrasound is the first-line exam for locating abnormal parathyroid during pregnancy (sensitivity of 69%, specificity of 94%) [1]. In patients with calcium levels higher than 12 mg/dL, such as our case, it is unusual for imaging studies to be unsuccessful.

Magnetic resonance imaging (MRI) has relatively low sensitivity detecting normally located or ectopic parathyroid adenomas [5] and was not performed.

Surgery

There are no current guidelines for the treatment of hyperparathyroidism in pregnancy. The options are either a conservative attitude or surgery. The approach selected depends on the presence and severity of symptoms, the gestational age and the patient's preference.

Mild PHPT with mild elevation in maternal calcium levels can be monitored, but clinically significant disease should be operated[7,8].

The timing of surgical treatment of PHPT is a central finding. Since the majority of pregnancies are lost between weeks 10 and 15, it may be appropriate to operate early in the second trimester, especially in patients with calcium levels exceeding 11.4 mg/dL and in those with a previous history of pregnancy loss[8].

Several studies have considered that surgery in the second trimester is safe for both mother and fetus but their results are based on a small number of patients[3].

Another study reported that third trimester parathyroidectomy is much safer than previously assumed, with reported fetal complications as low as 5.9%. Consequently, a widening of the recommended window for surgery has been proposed [10].

Minimally invasive approaches have gained progressive acceptance over the past two decades as a safe and effective alternative technique, owing to the use of preoperative imaging either with neck ultrasound or sestamibi scintigraphy to suggest or mark, respectively, the position of the parathyroid glands. The negative imaging prior to the surgery is not an absolute contraindication for neck exploration surgery, even in pregnancy [5].

Our patient chose to delay neck surgery to after the delivery. Options for medical management were therefore explored.

Medical treatment

The efficacy and safety of medical management for PHPT in pregnancy are unknown. Hydration and calcitonin have emerged as safe treatments but are considered ineffective for long-term serum calcium control [6]. Intravenously or orally administered hydration (with or without forced diuresis) is the first line of treatment [8]. Furosemide crosses the placenta and adverse events have been observed in animal reproduction studies [11].

Calcitonin may cause prompt reduction in calcium levels when administered intravenously or intramuscularly, but it is not a viable option for prolonged treatment, since tachyphylaxis rapidly develops [4]. For that reason, calcitonin was not administered in this patient.

The use of cinacalcet during pregnancy is debated [6]. Cinacalcet is a calcimimetic agent that binds to the calcium- sensing receptor (CaSR), activating CaSR to react to the extracellular calcium concentration and decrease PTH secretion. It is effective in all forms of hyperparathyroidism but is mainly used for the treatment of secondary hyperparathyroidism and parathyroid carcinoma [12]. As CaSRs are present in the placenta, cinacalcet may alter placental function and potentially induce fetal and neonatal hypocalcemia. Its use is limited by the lack of data on the fetus and new-born but animal studies did not show embryonal or fetal toxicity [13].

The use of cinacalcet for treatment of PHPT in pregnancy was reported [6,13]. No adverse fetal effects were reported but in one case the benefit of cinacalcet was weak [6].

Bisphosphonates are commonly used in the treatment of osteoporosis, hypercalcemia, and other conditions characterized by excessive bone resorption. They are incorporated into active bone remodelling sites and suppress bone turnover by inhibiting bone mineral breakdown. Consequently, there is a decrease in calcium release and levels of serum calcium, an increase in bone mineral density, and an improvement in bone quality [12].

Bisphosphonates cross the placenta. Studies on animals have associated gestational exposure to bisphosphonates to decreased fetal bone growth, decreased fetal survival and decreased birth weight. Nonetheless, there is a lack of data on its use in pregnant women or in women of childbearing age. In addition, the bisphosphonate doses used in animal studies are generally much higher than those used in humans [14].

There are a few published data on women exposed to bisphosphonates during pregnancy. Stathopoulos et al. identified 78 foetus whose mothers took bisphosphonates before or during the pregnancy. Sixty-nine gestations resulted in live births while 9 abortions were reported. All of those were attributed to maternal concomitant disease and medications. There were at least 33 cases of women that received treatment with bisphosphonates during the first 3 months of pregnancy and four cases of women who received bisphosphonates after 28 weeks' gestation. Two neonates had transient hypocalcemia after delivery. None of the new-borns presented with serious adverse events [14].

Green et al found 9 published cases of women taking pamidronate prior to pregnancy and 5 cases during pregnancy. Of the latter, 4 were in the 2nd and 3rd trimesters of pregnancy and the neonatal adverse events described were transient hypercalcaemia and hypocalcemia (1 case each) [15].

In our case, we chose to use bisphosphonates (pamidronate) because of its superior efficiency compared to cinacalcet and its previous use in pregnant women to treat hypercalcemia.

Conclusion

our case of primary hyperparathyroidism during pregnancy highlights the difficulty in locating anomalous parathyroid(s). After the surgical option was refused by the patient, the choice of medical treatment was challenging, and deciding on the most balanced medical treatment to control maternal calcium levels without fetal harm was essential. The use of loop diuretics and bisphosphonates proved to be effective in controlling hypercalcemia until the end of pregnancy without fetal or neonatal complications.

References

1. Dochez V, Ducarme G. Primary hyperparathyroidism during pregnancy. Arch Gynecol Obstet. 2015 Feb;291(2):259–263.
2. Hirsch D, Kopel V, Nadler V, Levy S, Toledano Y, Tsvetov G. Pregnancy outcomes in women with primary hyperparathyroidism. J Clin Endocrinol Metab. 2015 May;100(5):2115–2122.
3. Abood A, Vestergaard P. Pregnancy outcomes in women with primary hyperparathyroidism. Eur J Endocrinol. 2014 Jul;171(1):69–76.
4. Marcocci C, Cetani F. Clinical practice. Primary hyperparathyroidism. N Engl J Med. 2011 Dec 22;365(25):2389–2397.
5. Diaz-Soto G, Linglart A, Sénat M-V, Kamenicky P, Chanson P. Primary hyperparathyroidism in pregnancy. Endocrine. 2013 Dec;44(3):591–597.
6. Vera L, Oddo S, Di Iorgi N, Bentivoglio G, Giusti M. Primary hyperparathyroidism in pregnancy treated with cinacalcet: a case report and review of the literature. J Med Case Reports. 2016 Dec 20;10(1):361.
7. Truong MT, Lalakea ML, Robbins P, Friduss M. Primary hyperparathyroidism in pregnancy: a case series and review. The Laryngoscope. 2008 Nov;118(11):1966–1969.
8. Norman J, Politz D, Politz L. Hyperparathyroidism during pregnancy and the effect of rising calcium on pregnancy loss: a call for earlier intervention. Clin Endocrinol (Oxf). 2009 Jul;71(1):104–109.
9. Chamarthi B, Greene MF, Dluhy RG. Clinical problem-solving. A problem in gestation. N Engl J Med. 2011 Sep 1;365(9):843–848.
10. Schnatz PF, Thaxton S. Parathyroidectomy in the third trimester of pregnancy. Obstet Gynecol Surv. 2005 Oct;60(10):672–682.
11. Riva E, Farina P, Tognoni G, Bottino S, Orrico C, Pardi G. Pharmacokinetics of furosemide in gestosis of pregnancy. Eur J Clin Pharmacol. 1978 Dec 18;14(5):361–366.
12. Rey E, Jacob C-E, Koolian M, Morin F. Hypercalcemia in pregnancy - a multifaceted challenge: case reports and literature review. Clin Case Rep. 2016 Oct;4(10):1001–1008.
13. Horjus C, Groot I, Telting D, van Setten P, van Sorge A, Kovacs CS, Hermus A, de Boer H. Cinacalcet for hyperparathyroidism in pregnancy and puerperium. J Pediatr Endocrinol Metab JPEM. 2009 Aug;22(8):741–749.
14. Stathopoulos IP, Liakou CG, Katsalira A, Trovas G, Lyritis GG, Papaioannou NA, Tournis S. The use of bisphosphonates in women prior to or during pregnancy and lactation. Horm Athens Greece. 2011 Dec;10(4):280–291.
15. Green SB, Pappas AL. Effects of maternal bisphosphonate use on fetal and neonatal outcomes. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm. 2014 Dec 1;71(23):2029–2036.