

## CASE REPORT

### Successful management of Pseudohypoparathyroidism Type 1b in pregnancy: a case report

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## ABSTRACT

Pseudohypoparathyroidism (PHP) refers to broad spectrum of genetic diseases characterized by the peripheral resistance to parathormone (PTH). This condition leads to hypocalcaemia, hyperphosphatemia and elevated PTH concentrations. There is scant literature on PHP in pregnancy, only nine cases published. The treatment of the disease in pregnant women is challenging. The main target is to avoid hyper/hypocalcemia in order to prevent maternal adverse effects and to protect the development of the fetal parathyroid glands. We report a rare case of PHP type 1b in a pregnant woman, managed by a multidisciplinary team and treated with a tailored therapy.

**KEYWORDS:** hypercalcemia, hypocalcemia, parathormone, pregnancy, pseudohypoparathyroidism.

## **INTRODUCTION**

Pseudohypoparathyroidism (PHP) includes a group of heterogeneous endocrine disorders characterized by end-organ unresponsiveness to parathormone (PTH) (1). PTH controls calcium and phosphorus serum concentration through an intricate mechanism also involving Vitamin D. There are several variants of PHP according to the pathogenesis of the disease. The involved gene is *GNAS1*, an imprinted gene in humans; the allele expression for a specific tissue depends on whether the allele is inherited from the mother or from the father. *GNAS1* encodes for the alpha-subunit of the G protein, that mediates the mechanism of action of PTH and other G-protein coupled hormones (2).

Patients affected by PHP type 1a present varying degrees of Albright's hereditary osteodystrophy (AHO) features, a typical phenotype characterized by a round face, short stature, skeletal abnormalities, obesity, heterotopic calcifications, and developmental delay (3). Patients with PHP type 1b shows isolated PHT resistance, without AHO (4).

There is scant literature available for PHP in pregnancy, with only one case reported of PHP type 1b (5), four cases of PHP type 1 a (4, 6-8), one case of PHP type 2 (9) and three cases of unspecified PHP (1, 10).

PHP management is challenging in pregnancy, in order to maintain maternal normocalcemia while providing an adequate calcium supply to the fetus. Pregnancy is commonly associated with modified calcium metabolism, due to the reduction of serum albumin and active placental calcium transport to supply fetal request (11).

It remains debated whether the calcium and calcitriol supplementations are useful, because in some cases the levels seemed to be normalized during pregnancy (10). Conversely, in other reported cases, calcium or vitamin D levels fell during pregnancy (1, 5-9) and medications were necessary.

## **CASE REPORT**

A 40-years-old 3G1P pregnant woman affected by PHP 1b was referred to Santo Stefano Hospital in Prato (Italy) at 17 weeks of her third pregnancy. During her second gestation she experienced osteoporosis and the labour was complicated by a tetanic crisis which led to an emergency

caesarean section (CS); a male baby was delivered with a pH 6,96 and a physiological neonatal follow up was recorded up to a year.

In the preconceptional period she was taking calcium citrate 1 gr and Calcitriol 0,50 mg. During pregnancy, the dosage was increased to calcitriol 1,25 mg per day, and 4 -6 gr of calcium carbonate, because of paresthetic symptoms. Blood tests showed Calcium 9,5 mg/dl, 25(OH) vit. D 28,7 ng/ml, PTH 428 pg/ml, TSH 3,535 mU/L, Ft4 0,55ng/dl, Ft3 3,04 pg/ml, TPO Ab 0,3UI/L, Tg AB <0,9 UI/L, magnesium 1.3 mg/dl. The therapy was optimized by changing calcium carbonate with 2 g of oral liquid calcium citrate and 2,25 g of oral magnesium. In addition, levothyroxine was prescribed to correct hypothyroxinemia. Moreover, the patient suffered from panic attacks and anxiety that led the psychiatrist to administer Olanzapine 2.5 mg daily.

The CS was scheduled at 38 weeks of gestation; a healthy female was delivered with a birth weight of 2990 gr, an Apgar score of 9-10 and a pH of 7.32.

Maternal serum and ionized calcium were checked during the fasting period before surgery, when the patient could not take her oral supplementation of calcium citrate and calcitriol. The pre-operative serum calcium level was 7.7 mg/dL and two vials of calcium gluconate were administered in 250 cc of sodium chloride with a velocity of infusion of 50 mL/h till the end of the fasting period.

After the CS serum and ionized calcium levels of the patient were normal (8.9 mg/dL and 1.14 mmol/L, respectively) and the oral therapy with calcium citrate and calcitriol was restarted. The course of the puerperium was uncomplicated; the patient never experienced symptoms of hypocalcemia and she started breastfeeding. She was discharged 4 days after the CS in good conditions, with normal levels of serum and ionized calcium (7.9 mg/dL and 1.24 mmol/L, respectively). The baby had a normal level of serum calcium and a decreasing PTH-level during the first days of life, and he was discharged in good general health conditions.

## **DISCUSSION**

Management of pregnant women affected by PHP is difficult because it is rarely reported in literature. Parathormone controls calcium and phosphorus serum concentration through an intricate mechanism that also involves Vitamin D, so the end-organ resistance leads to hypocalcaemia, hyperphosphatemia and elevated PTH concentrations.

Maternal hypocalcemia and hypercalcemia may also impact fetal parathyroid development, resulting in maternal and fetal possible increased morbidity. In case of maternal hypercalcemia, calcium placental transfer is increased, and it may result in suppression of the fetal parathyroid glands. Conversely, in presence of maternal hypocalcemia, calcium placental transfer is decreased, and it may result in fetal parathyroids glands stimulation. This condition may lead to fetal hyperparathyroidism with severe cases presenting with subperiosteal bone resorption, bowing of the

long bones, osteitis fibrosa cystica, intrauterine rib and limb fractures, low birth weight, spontaneous abortion, and fetal death.

Although several case reports have described calcium serum and PTH normalization within the first month after birth, intrauterine hyperparathyroidism has been associated with skeletal demineralization and intrauterine fractures. Besides, intrauterine hypocalcemia and hypoparathyroidism have been associated with risk of abortion and neonatal tetany (12).

In women with PHP the objective is to prevent maternal hypocalcemia, supplying the fetus with an adequate amount of calcium. However, it is still debated whether calcium and calcitriol supplementation is necessary or not.

In the case described the patient had poor compliance to therapy with the high dose of calcium carbonate because she experienced gastric symptoms. This led to a "self-reduction" of the therapy exacerbating paraesthesia and mental distress in relation to the higher risk of another complicated pregnancy. Besides calcium carbonate supplementation was inappropriate and excessive also for the fetus (13). We checked the patient every two-three weeks and we managed to target serum calcium level toward the lower part of the normal range with 2-2,5 gr of calcium citrate per day.

Giving the minimum effective dose of calcium, the main target of the therapy was to avoid both maternal hyper/hypocalcemia and adverse effects on the development and function of fetal parathyroid glands.

According to the cases described by O'Donnell et al. (1), Ghershberg et al. (6), Singh et al. (7), Ochiai et al. (8), Saito and Saito (9), our patient required calcium dosage implementation during third trimester because of maternal hypocalcemia; conversely, Guedes Ramallo et al. (4) and Seki et al. (5) reported cases in which the level of calcium was maintained normal for all the duration of pregnancy.

In our experience vitamin D remained stable since the beginning of gestation, in accordance with the findings of Guedes Ramallo et al. (4) and Ochiai et al. (8). However, Seki et al. (5) reported a case in which level of vitamin D decreased during late pregnancy, while Breslau et al. (10) described a case with an increasing of vitamin D level during mid- and late pregnancy, so vitamin D supplementation was not requested.

Regarding our case of type PHP 1b, it differs from the only one case of PHP type 1b reported by Seki et al. (5), because our patient experienced hypocalcemia and stable level of vitamin D, while Seki et al. described a case with normocalcemia and decreasing of vitamin D level during pregnancy. This discrepancy between the cases reported in literature may be due to the heterogeneity of manifestation of PHP, reflecting the broad spectrum of genetic and epigenetic defects of the GNAS gene that may influence calcium metabolism. Besides in healthy women placenta produces calcitriol with a mechanism of regulation that is still unknown; in women with PHP the placental calcitriol production rate is not significantly different from that of normal placentas (14).

The surveillance of pregnant women with PHP is also necessary during labour and lactation: in fact, hyperventilation during labour leads to alkalosis, facilitating the binding between calcium and serum protein, causing hypocalcemia. Moreover, during breastfeeding, mammary tissue produces PTH-related protein (PTHrp), which increases bone resorption and renal calcium reabsorption to supply milk production (15).

## **CONCLUSION**

Management of pregnant patients affected by PHP is still controversial; what we know is that adequate calcium and calcitriol supplementation in patients at major risk of hypocalcemia is necessary to obtain good maternal and perinatal outcomes. In our case we conducted a strict surveillance on the patient since she came to the antenatal clinic, involving endocrinologists, psychiatrists, anaesthesiologists and pediatricians. She often checked calcium serum level, in order to adjust values and to reach the best therapy for the patient and the fetus.

Therefore, good compliance with therapy, regular biochemical and clinical monitoring and a multidisciplinary management are probably the best way to manage this condition in pregnancy. However, there is scant literature about PHP in pregnancy, so more data are necessary to establish the best management of these patients.

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