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

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### ABSTRACT

**Background.** 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/hypocalcaemia in order to prevent maternal adverse effects and to protect the development of the foetal parathyroid glands.

**Case presentation.** We report a rare case of PHP type 1b in a pregnant woman, managed by a multidisciplinary team and treated with a tailored therapy.

**Conclusions.** Good compliance with therapy, regular biochemical and clinical monitoring, and a multidisciplinary management are probably the best way to manage this condition in pregnancy.

### 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

intricated 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 1a [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 foetus. Pregnancy is commonly associated with modified calcium metabolism, due to the reduction of serum albumin and active placental calcium transport to supply foetal 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 PRESENTATION

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 g and Calcitriol 0.50 mg. During pregnancy, the dosage was increased to calcitriol 1.25 mg per day, and 4-6 g 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 0.55 ng/dL, Ft3 3.04 pg/mL, TPO Ab 0.3 UI/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 hypothyroxinaemia. 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 2,990 g, 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 hypocalcaemia 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 hypocalcaemia and hypercalcemia may also impact foetal parathyroid development, resulting in maternal and foetal possible increased morbidity. In case of maternal hypercalcemia, calcium placental transfer is increased, and it may result in suppression of the foetal parathyroid glands. Conversely, in presence of maternal hypocalcaemia, calcium placental transfer is decreased, and it may result in foetal parathyroids glands stimulation. This condition may lead to foetal 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 foetal 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 hypocalcaemia and hypoparathyroidism have been associated with risk of abortion and neonatal tetany [12].

In women with PHP the objective is to prevent maternal hypocalcaemia, supplying the foetus 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 foetus [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 g of calcium citrate per day.

Giving the minimum effective dose of calcium, the main target of the therapy was to avoid both maternal hyper/hypocalcaemia and adverse effects on the development and function of foetal parathyroid glands. According to the cases described by O'Donnel *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 hypocalcaemia; 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 hypocalcaemia 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 products 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 hypocalcaemia. Moreover, during breastfeeding, mammary tissue produces PTH-related protein (PTHrp), which increases bone resorption and renal calcium reabsorption to supply milk production [15].

## CONCLUSIONS

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 hypocalcaemia 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 paediatricians. She often checked calcium serum level, in order to adjust values and to reach the best therapy for the patient and the foetus. 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.

## COMPLIANCE WITH ETHICAL STANDARDS

### *Authors contributions*

A.F.C., A.V., A.M.M.: Conceptualization. L.G., M.G, V.P., V.N., L.M.: Formal analysis. A.V., A.M.M.: Writing – original draft. A.V., M.P., I.T.: Writing – review & editing. A.F.C., P.V., M.P.: Supervision. All authors have read and agreed to the published version of the manuscript.

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**Disclosure of interests**

The authors declare that they have no conflict of interests.

**Ethical approval**

N/A (the clinical management described it's part of normal clinical practice).

**Informed consent**

General informed consent for surgical procedure (CS) was obtained from the patient, as required by normal clinical practice.

**Data sharing**

Data are available under reasonable request to the corresponding author.

**REFERENCES**

- O'Donnell D, Costa J, Meyers AM. Management of pseudohypoparathyroidism in pregnancy. Case report. *Br J Obstet Gynaecol.* 1985;92(6):639-41. doi: 10.1111/j.1471-0528.1985.tb01405.x.
- Hayward BE, Kamiya M, Strain L, Moran V, Campbell R, Hayashizaki Y, Bonthron DT. The human GNAS1 gene is imprinted and encodes distinct paternally and biallelically expressed G proteins. *Proc Natl Acad Sci U S A.* 1998 18;95(17):10038-43. doi: 10.1073/pnas.95.17.10038.
- Albright F, Burnett CH, Smith PH, Parsons W. Pseudohypoparathyroidism, an example of "Seabright-Bantam Syndrome"; Report of Three Cases. *Endocrinology.* 1942;30:922-32.
- Guedes Ramallo P, Boix Carreño E. Management of pseudohypoparathyroidism in pregnancy: a case report. *J Obstet Gynaecol.* 2017;37(4):519-20. doi: 10.1080/01443615.2016.1250733.
- Seki K, Osada H, Yasuda T, Sekiya S. Pseudohypoparathyroidism type 1b in pregnancy. *Gynecol Obstet Invest.* 1999;47(4):278-80. doi: 10.1159/000010122.
- Gershberg H, Weseley AC. Pseudohypoparathyroidism and pregnancy. Is pseudo-pseudohypoparathyroidism a mild form of pseudohypoparathyroidism? *J Pediatr.* 1960;56:383-6. doi: 10.1016/s0022-3476(60)80190-4.
- Singh A, Agarwal N, Chopra S, Sikka P, Suri V, Kumar B, et al. Management of Pseudohypoparathyroidism Type 1a during Pregnancy and Labor: A Case Report. *Case Rep Obstet Gynecol.* 2012;2012:629583. doi: 10.1155/2012/6295833.
- Ochiai D, Uchino H, Ikeda T, Yakubo K, Fukuiya T. Pseudohypoparathyroidism type 1a in pregnancy. *J Obstet Gynaecol.* 2013;33(8):900. doi: 10.3109/01443615.2013.834302.
- Saito H, Saito T. Latent pseudohypoparathyroidism type II: risk of insufficiency of calcium metabolism during pregnancy. *Horm Metab Res.* 1988;20(11):725. doi: 10.1055/s-2007-1010930.
- Breslau NA, Zerwekh JE. Relationship of estrogen and pregnancy to calcium homeostasis in pseudohypoparathyroidism. *J Clin Endocrinol Metab.* 1986;62(1):45-51. doi: 10.1210/jcem-62-1-45.
- Croley TE. The intracellular localization of calcium within the mature human placental barrier. *Am J Obstet Gynecol.* 1973;117(7):926-32. doi: 10.1016/0002-9378(73)90063-x.
- Khan AA, Clarke B, Rejnmark L, Brandi ML. Management of endocrine disease: Hypoparathyroidism in pregnancy: review and evidence-based recommendations for management. *Eur J Endocrinol.* 2019;180(2):R37-R44. doi: 10.1530/EJE-18-0541.
- Mantovani G. Clinical review: Pseudohypoparathyroidism: diagnosis and treatment. *J Clin Endocrinol Metab.* 2011;96(10):3020-30. doi: 10.1210/jc.2011-1048.
- Zerwekh JE, Breslau NA. Human placental production of 1 alpha,25-dihydroxyvitamin D3: biochemical characterization and production in normal subjects and patients with pseudohypoparathyroidism. *J Clin Endocrinol Metab.* 1986;62(1):192-6. doi: 10.1210/jcem-62-1-192.
- Kovacs CS. Calcium and bone metabolism disorders during pregnancy and lactation. *Endocrinol Metab Clin North Am.* 2011;40(4):795-826. doi: 10.1016/j.ecl.2011.08.002.