Humoral hypercalcemia of pregnancy treated with bisphosphonates

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SUMMARY

Hypercalcemia can be hazardous during pregnancy, most cases being due to primary hyperparathyroidism. We report a case of hypercalcemia with suppressed PTH levels necessitating treatment with bisphosphonates during pregnancy. A 38-year-old woman at the 26th week gestation was admitted because of symptomatic hypercalcemia. She did not take any medication that could influence her calcium levels. Physical examination was unremarkable. Laboratory tests on admission were: calcium 12.7 mg/dL (8.5-10.5 mg/dL), phosphorus 1.8 mg/dL (2.5-4.5 mg/dL) and PTH on 3 consecutive tests 1.2, 1.3 and 1.2 pg/mL (15-65 pg/mL). Her 24h urine calcium was 900 mg, 25-OH-D 40 ng/mL (30-58 ng/mL) and 1,25-OH-D 99 pg/mL (80-146 for women in the third trimester). Abdominal ultrasound revealed multiple hypervascular liver lesions consistent with hemangiomas by MRI. Breast and neck ultrasound were normal, and chest CT revealed few non-significant 0.3-0.7 cm pulmonary nodules with no change after an interval of 3 months. She was treated with isotonic saline, loop diuretics and calcitonin. Despite this treatment, calcium levels remained high (14.1 mg/dL), and pamidronate was initiated. On 35th week gestation, she underwent a cesarean section complicated by hypocalcemia of the newborn. Eight weeks after delivery, her calcium levels are 9.4 mg/dL and PTH 18 mg/dL. According to the extensive workup and the post-partum normalization of PTH and calcium levels, we conclude that excessive secretion of placental PTHrP was the cause of hypercalcemia in this patient. No significant adverse effect of bisphosphonate on the mother or baby were seen at the short term follow up. Arch Endocrinol Metab. 2018;62(1):125-8

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INTRODUCTION

Hypercalcemia can be hazardous during pregnancy, leading to maternal and fetal complications. Hypercalcemia is challenging to diagnose during this period because physiological changes such as hemodilusion, hypoalbuminemia, an elevated glomerular filtration rate, hypercalciuria and placental transfer of calcium to the fetus may all lead to lower blood calcium levels. Most cases of hypercalcemia diagnosed during pregnancy are due to primary hyperparathyroidism (PHPT) caused by a solitary adenoma. Less commonly, hypercalcemia is caused by multiple parathyroid adenomas, diffuse hyperplasia and parathyroid carcinoma (1). When maternal PTH levels are suppressed, the diagnostic challenge is further increased. Several cases have been reported of women with hypercalcemia secondary to milk alkali syndrome (2,3), and cases of parathyroid-related-protein (PTHrP) mediated hypercalcemia have been described during pregnancy in women with uterine leiomyoma (4), neuroendocrine tumor of the pancreas (5) and ovarian clear cell carcinoma (6). Rare cases of humoral hypercalcemia of pregnancy, in which the PTHrP source was suspected to be the placenta, have also been described previously in the literature (7,8).

It is probable that most cases of hypercalcemia due to PHPT go unrecognized and are not associated with maternal or fetal complications (9). When symptomatic, women can present with nausea, vomiting, confusion, agitation, nephrolithiasis, pancreatitis, hyperemesis gravidarum and preeclampsia. Hypercalcemic crisis has been reported with calcium levels above 14 mg/dL leading to uremia, coma and maternal death. The most serious fetal complications involve suppressed parathyroid gland with severe hypocalcemia, tetany and fetal or neonatal demise (10-13).

We report a case of hypercalcemia with suppressed parathyroid hormone (PTH) levels necessitating treatment with bisphosphonates during pregnancy.

CASE REPORT

A 38-year-old woman at the 26th week gestation was admitted to hospital because of elevated calcium levels. Her first pregnancy 16 years prior to presentation was uneventful. She was a carrier of the hemophilia gene and was generally healthy. Her symptoms consisted of pruritus, polidypsia and polyuria. She did not take any medication or food supplement that could influence her calcium levels. Physical examination was unremarkable. Laboratory tests were as follows: calcium 12.7 mg/dL (reference range, 8.5-10.5 mg/dL), albumin 3.6 mg/dL (3.5-5.2 g/dL), ionized calcium 7.9 mg/dL (4-4.9), magnesium 1.21 (1.8-2.6 mg/dL), phosphorus 1.8 mg/dL (2.5-4.5 mg/dL) and PTH levels on 3 consecutive tests 1.2, 1.3 and 1.2 pg/mL (15-65 pg/mL). Her 24h urine calcium was 900 mg, 25-hydroxyvitamin (25OH) D- 40 ng/mL (30-58 ng/mL), 1,25OH vitamin D- 99 pg/mL (16-80 pg/mL for the general population, 80-146 for women in the third trimester (14). Thyroid function tests and angiotensin-converting enzyme levels were normal. Further evaluation included abdominal ultrasound, which revealed multiple hypervascular liver lesions that were later diagnosed as liver hemangiomas by MRI; breast and neck ultrasounds, which were normal; and chest CT, which revealed small pulmonary nodules (0.3-0.7 cm) that had not changed at a follow up study 3 months afterward. She was treated with isotonic saline (up to 250 mL/hour) and loop diuretics (40 mg/day) and received calcitonin (300 units twice a day, than 200 units twice daily for 2 days). Urinary output reached 13.5 liter/day. Since calcium levels rose up to 14 mg/dL (corrected to albumin) after this vigourus therapy, treatment with pamidronate was initiated. A total of 90 mg was given in three divided doses with a good response. At the 35th week gestation, after calcium levels began to rise again, induction of delivery was ensued. Due to no progression, she underwent a cesarean section complicated by hypocalcemia of the newborn. Eight weeks after delivery, her calcium levels were 9.4 mg/dL, phosphorus 3.4, 1,25 OH vitamin D 49 mg/dL and PTH 18 pg/mL. Four months after delivery, maternal and infant's calcium levels were within the normal range, and the infant's height and weight growth were adequate.

DISCUSSION

Regulation of calcium and phosphorus during fetal life is of utmost importance for proper bone development and mineralization. This regulation is dependent on maternal PTH and PTHrP (15). During pregnancy, maternal intestinal absorption of calcium more than doubles as a response to the increasing demand. Factors responsible for this are calcitriol and placental lactogen among other things. Several changes become apparent more obviously during the 3rd trimester and during lactation: free calcitriol levels rise (16), maternal bone resorption becomes evident (due to an increase in urine cross-linked N-telopeptides of type I collagen, especially during the winter) (17), and PTHrP levels, which rise steadily during pregnancy, undergo further elevation during lactation (18).

PTHrP can be secreted physiologically from the lactating breast, placenta, pregnant uterus and various benign and malignant tumors. It has an effect on chondrocyte differentiation and an anabolic function on bone. PTHrP signaling is required for the formation of the mammary glands and is related to calcium transfer across the placenta (19). PTHrP can reach the circulation and cause hypercalcemia (7,20). Its role in maternal bone resorption and osteoporosis of pregnancy and lactation has not been elucidated yet (16,21).

After the extensive workup, and in view of the normalization of calcium levels after delivery, it is our opinion that the cause of the presented patient's hypercalcemia was overproduction of PTHrP in the placenta. It is possible that PTHrP was secreted from mammary glands, or from another unrevealed source. Another possibility is that this is a case of aberrant calcium homeostasis not related to pregnancy. Unfortunately, PTHrP measures are unavailable to us.

Calcitriol levels rise during normal pregnancy. PTH is normally the dominant regulator of Cyp27b1 in adults. During pregnancy the marked increase in calcitriol occurs while PTH is often suppressed to low levels, which suggests that PTH is not responsible for the upregulation of Cyp27b1 (22). Reference values for pregnancy have been suggested and are significantly higher than for the general population and even higher during the third trimester (14).

It is suggested that estradiol, prolactin and placental lactogen, which are elevated during pregnancy, may in part stimulate Cyp27b1, as suggested by animal data. Although the placenta was previously considered to be the source of calcitriol during pregnancy, it is nowadays believed that it is mainly secreted from the maternal kidney (23). In the present case calcitriol levels were not elevated when compared to pregnancy reference values, and hence, it is our view that PTHrP might be a reasonable explanation for the hypercalcemia presented in this case. Other pregnancy-related hormones working excessively or aberrantly might have been the culprit, but the limited laboratory possibilities prevented us from reaching the final conclusion.

Bisphosphonates are synthetic analogues of pyrophosphate that inhibit bone resorption. They are absorbed into the mineral surface of the bone where they interfere with the action of osteoclasts (24). The slow release of bisphosphonates from the bone causes detectable levels in urine for many weeks and months after discontinuing the drug (25).

Bisphosphonates are not considered an accepted treatment during pregnancy, as animal studies found adverse effects on the fetus's skeleton. In rats, bisphosphonates were found to cross the placenta, accumulate in the skeleton of the fetus and decrease fetal weight and bone growth (26). It was also shown to cause symptomatic hypocalcemia of the dams and even fetal demise (27). It is noted that doses administered in animal studies were much higher than those used in clinical practice.

Data regarding the effects of bisphosphonates on human reproduction are scarce. Case reports of inadvertent exposure during pregnancy or pre-pregnancy administration had no apparent adverse effect on the embryo or fetus, although the newborn can develop hypocalcemia in the first few days of life (28). In a review of 65 maternal-fetal pairs with a wide variety of agents and doses, bisphosphonates were related to a small decrease in gestational age and birthweight and hyper or hypocalcemia of the newborn. No long-term maternal or neonatal adverse effects were reported (29). In this case, decision making was established by a multidisciplinary team constituted by endocrinologists, gynecologists, a nephrologist and a clinical pharmacologist. As calcium levels were elevated and tended to further increase despite the reception of accepted treatment, it seemed prudent to make another, more significant intervention even though the data was not sufficient.

In conclusion, hypercalcemia during pregnancy constitutes a diagnostic and management challenge. We add our experience in evaluating hypercalcemia with decreased PTH levels and the use of bisphosphonates during pregnancy with good results.

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