Hypercalcemia during Pregnancy, Puerperium, and Lactation: Review and a Case Report of Hypercalcemic Crisis after Delivery Due to Excessive Production of PTH-related Protein (PTHrP) without Malignancy (Humoral Hypercalcemia of Pregnancy)

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Abstract. Hypercalcemia during pregnancy or after delivery is uncommon, and mostly associated with primary hyperparathyroidism (PHPT). If unrecognized, it may increase maternal and fetal morbidity. In a very few patients with PHPT, hypercalcemic crisis develops during pregnancy and particularly after delivery, since calcium transport from the mother to the fetus is abruptly disrupted. Hypercalcemia may also develop in pregnant women due to PTH-related protein (PTHrP)-producing malignant tumors (humoral hypercalcemia of malignancy). Since PTHrP is produced physiologically in fetal and maternal tissues, hypercalcemia may occasionally develop during pregnancy, puerperium, and lactation due to excessive production of PTHrP in the placenta and/or mammary glands. PTHrP may also be involved in milk-alkali syndrome that develops during pregnancy. Although non-malignant hypercalcemia is usually mild, we report a 28-years-old pregnant woman who developed hypercalcemic crisis after normal delivery of an infant. On the first postpartum day, the corrected serum calcium concentration increased to 19.4 mg/dl with a markedly increased serum level of PTHrP (28.4 pmol/L) (normal <1.1 pmol/L). After administration of saline and pamidronate, the serum levels of calcium and PTHrP rapidly normalized. Extensive examination revealed no malignant lesion, suggesting that the placenta may have been producing an excessive amount of PTHrP (humoral hypercalcemia of pregnancy). We review case reports of non-malignant hypercalcemic crisis associated with pregnancy indexed in PubMed in which serum levels of intact PTH and/or PTHrP were described, and stress that rapid control of hypercalcemia is mandatory to save the life of the mother and the infant.

Key words: Hypercalcemia, Hypercalcemic crisis, Hyperparathyroidism, Parathyroid hormone-related protein (PTHrP), Pregnancy

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PTHrP is produced physiologically in a number of fetal and maternal tissues, particularly in the placenta during pregnancy and in the mammary glands during lactation. In a non-lactating woman with massive mammary hyperplasia, hypercalcemia due to an increased expression of PTHrP in the mammary gland has been reported [13]. Similarly, hypercalcemia due to an increased serum level of PTHrP has been reported during lactation in the puerperal period [14]. Similar cases have also been reported in some patients with postpartum osteoporosis. Milk-alkali syndrome may also occur during pregnancy, occasionally accompanied by an elevated serum level of PTHrP.

Although PTHrP-associated hypercalcemia during pregnancy or in lactating women is usually mild, we report a pregnant woman who developed hypercalcemic crisis after normal delivery of an infant at 33 weeks of gestation. The markedly increased serum levels of calcium and PTHrP decreased rapidly in the postpartum period. An extensive survey was unable to demonstrate any benign or malignant tumor. Although this case was briefly reported in a Japanese commercial journal [15], the relevant abstract presented at the Annual Meeting of the American Society for Bone and Mineral Research [16] was quoted in Williams Textbook of Endocrinology [17]. Since the journal was not indexed in PubMed, the clinical courses of the mother and the newborn are described here in more detail after approval by the Editorial Board of the Endocrine Journal.

Furthermore, we review non-malignant cases of hypercalcemic crisis in pregnant women (Table 1), and discuss the pathophysiology and treatment.

### Calcium metabolism in Pregnancy

During pregnancy, more than 20 g of calcium is transported from the mother into the fetus through the placenta [1, 18]. Calcium ions cross the placenta freely and rapidly from the maternal to the fetal circulation [2]. PTH has no effect on placental calcium transport [1]. Calcium transport in the placenta is stimulated by PTHrP(1-141) and the midmolecule fragment of PTHrP(67-86), but not by PTH(1-34) or PTHrP(1-34), suggesting that PTHrP stimulates receptor(s) distinct from the PTH/PTHrP receptor [18, 19]. As a result of this active transport of calcium in the placenta, the

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age</th>
<th>Stage</th>
<th>Total Ca</th>
<th>P</th>
<th>Creatinine</th>
<th>PTH</th>
<th>PTHrP</th>
<th>infant</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PHPT</td>
<td>41</td>
<td>32 W*</td>
<td>19.4 mg/dl</td>
<td>ND</td>
<td>2.0 mg/dl</td>
<td>3659 pgEq/L (150–375)</td>
<td>ND</td>
<td>stillborn</td>
<td>[22]</td>
</tr>
<tr>
<td>2. PHPT</td>
<td>26</td>
<td>31 W*</td>
<td>5 mmol/L</td>
<td>ND</td>
<td>2.5 mg/dl</td>
<td>1800 pmol/L (5–50)</td>
<td>ND</td>
<td>alive**</td>
<td>[23]</td>
</tr>
<tr>
<td>3. PHPT</td>
<td>28</td>
<td>21 W*</td>
<td>25.8 mg/dl</td>
<td>3.8 mg/dl (2.5–4.8)</td>
<td>2.0 mg/dl (0.4–1.5)</td>
<td>790 pg/ml</td>
<td>ND</td>
<td>alive (full term)</td>
<td>[24]</td>
</tr>
<tr>
<td>4. PHPT</td>
<td>19</td>
<td>8 W (15 W*)</td>
<td>3.99 mM</td>
<td>ND</td>
<td>141 μmol/L (&lt;106)</td>
<td>11.4 pmol/L (1.1–5.4)</td>
<td>ND</td>
<td>alive (full term)</td>
<td>[25]</td>
</tr>
<tr>
<td>5. PHPT</td>
<td>41</td>
<td>22 W*</td>
<td>20.0 mg/dl</td>
<td>ND</td>
<td>144 μmol/L (62–115)</td>
<td>712 pg/ml (7–53)</td>
<td>ND</td>
<td>alive (full term)</td>
<td>[26]</td>
</tr>
<tr>
<td>6. MAS</td>
<td>31</td>
<td>36 W</td>
<td>22.5 mg/dl</td>
<td>0.7 mg/dl</td>
<td>1.9 mg/dl</td>
<td>4 pg/ml (4–19)</td>
<td>ND</td>
<td>alive (full term)</td>
<td>[51]</td>
</tr>
<tr>
<td>7. MAS</td>
<td>35</td>
<td>35 W</td>
<td>4.0 mM*</td>
<td>0.58 mM (0.8–1.5)</td>
<td>0.19 mM (0.05–0.09)</td>
<td>0.66 pmol/L (1.3–6.8)</td>
<td>ND</td>
<td>alive**</td>
<td>[52]</td>
</tr>
<tr>
<td>8. MAS</td>
<td>38</td>
<td>37 W</td>
<td>4.0 mM</td>
<td>2.36 mg/dl</td>
<td>0.46 mM</td>
<td>0.8 pmol/L (1–7)</td>
<td>34.9 pmol/L</td>
<td>alive**</td>
<td>[53]</td>
</tr>
<tr>
<td>9. MAS</td>
<td>32</td>
<td>16 W</td>
<td>22 mg/dl (8.5–10.5)</td>
<td>0.8 mg/dl (2.5–4.5)</td>
<td>1.4 mg/dl (0.5–1.4)</td>
<td>1.0 mg/L (10–65)</td>
<td>0.3 pmol/L (&lt;0.5)</td>
<td>ND</td>
<td>[55]</td>
</tr>
<tr>
<td>10. HHP</td>
<td>28</td>
<td>33 W</td>
<td>19.4 mg/dl (8.5–10.5)</td>
<td>5.2</td>
<td>2.41 mg/dl (0.7–1.3)</td>
<td>&lt;5 pg/ml (23–73)</td>
<td>28.4 pmol/L (&lt;1.1)</td>
<td>alive (SD)</td>
<td>[**]</td>
</tr>
</tbody>
</table>

PHPT: primary hyperparathyroidism, MAS; milk alkali syndrome, HHP: humoral hypercalcemia of pregnancy; * ionized calcium concentration; 2.64 mmol (1.12–1.3 mmol/L), ** caesarian section, ND; not described, * parathyroidectomy, ** present case. SD; spontaneous delivery. Parentheses indicate reference ranges.
concentration of ionized calcium in the cord blood of the fetus is higher (5.5 ± 0.3 mg/dl; 1.37 ± 0.07 mmol/L) than that in normal adults (4.48–4.92 mg/dl; 1.12–1.23 mmol/L). The total calcium level is decreased in pregnant women due to hypoalbuminemia, but the ionized serum calcium level is not different from the normal adult level [1, 20].

When the placenta is removed from the newborn, the concentration of ionized calcium in the newborn falls to 4.0–4.7 mg/dl (1.00–1.17 mmol/L) in the first 1–2 days of life [20]. Plasma PTH levels are relatively low in the neonatal period and are minimally responsive to hypocalcemia during the first 2 to 3 days of life, leading to transient neonatal hypocalcemia. Infants born to mothers with prolonged hypercalcemia such as PHPT have a high incidence of symptomatic hypocalcemia [1], since prenatal parathyroid development has been suppressed for the entire period of pregnancy.

**Primary hyperparathyroidism**

The incidence of primary hyperparathyroidism in all woman of child-bearing age is estimated to be approximately eight new cases per 100,000 population per year [21]. If untreated, hypercalcemia is associated with an increased risk of maternal and fetal morbidity, and several cases of hypercalcemic crisis have been reported [22–26] (Table 1). Persistent maternal hypercalcemia suppresses the development of the fetal parathyroid glands. Therefore, the most frequent serious complications of maternal hypercalcemia are neonatal hypercalcemia, ranging from neonatal tetany to stillbirth.

In contrast to a newborn with hypocalcemia, the pregnant woman is at risk of hypercalcemic crisis after delivery. If the mother is untreated to term, sudden worsening of hypercalcemia can result from loss of the placenta and dehydration [3, 4, 23]. Therefore, while the neonate is at greater risk of tetany after delivery, the mother is also at greatest risk of hypercalcemic crisis during the same period [3].

There is a general consensus that parathyroidectomy should be performed during the second trimester in pregnant woman with symptomatic hyperparathyroidism [2–4]. Parathyroidectomy can also be performed safely even in the third trimester by an experienced parathyroid surgeon, when symptomatic hypercalcemia occurs [27].

However, symptom-free patients may be managed medically, allowing surgery to be postponed until after delivery [3].

**PTHrP-associated hypercalcemia**

**Malignancy-associated hypercalcemia (humoral hypercalcemia of malignancy)**

Parathyroid hormone-related protein (PTHrP) is produced by various malignant tumors. When produced excessively, a proportion of PTHrP enters the circulation, and stimulates the PTH/PTHrP receptor. Therefore, marked hypercalcemia develops through increased bone resorption and increased calcium reabsorption in the renal tubules, leading to humoral hypercalcemia of malignancy (HHM) [8]. Consequently, various cases of hypercalcemia during pregnancy have been reported [28, 29].

Metastatic breast carcinoma with hypercalcemia during pregnancy is fortunately extremely rare. Although bisphosphonate is contraindicated in pregnancy, intravenous administration of pamidronate is very effective in ameliorating severe hypercalcemia, without any apparent ill effects on the newborn [30, 31]. If a humanized neutralizing antibody against PTHrP is available, administration of such a monoclonal antibody would be a more efficient and safer treatment for these pregnant patients [32].

Similar to PTH, when the N-terminal fragment of PTHrP is infused into normal subjects, it stimulates 1α-hydroxylase in the renal tubules, leading to an increased serum level of active vitamin D (1,25-(OH)2D) [33]. However, in patients with HHM, the serum level of 1,25(OH)2D is not increased, but decreased in most cases for unknown reasons [8]. However, we have observed an increase in the conversion of 25OHD2 to 1,25(OH)2D in a patient with HHM in whom 1000 U vitamin D2 was inadvertently administered via intravenous hyperalimentation [34].

**Lactation-associated hypercalcemia**

PTHrP is synthesized by various fetal and adult tissues, particularly in the placenta during pregnancy and in the mammary glands during lactation [1]. Large amounts of PTHrP are also secreted into breast milk.
which contains $10^2$–$10^5$ the level of PTHrP in serum. When a large amount of PTHrP from the breast enters the bloodstream, it stimulates the movement of calcium from maternal bone into breast milk [36].

Therefore, when PTHrP is produced excessively in the mammary glands, hypercalcemia can develop, as has been reported in a woman with massive mammary hyperplasia [13]. Similarly, hypercalcemia with a slightly elevated serum level of PTHrP (1.12–2.21 pmol/L) has been reported in several women during lactation [14, 37–39]. Lactating women frequently have postpartum osteoporosis, and an increased serum level of PTHrP has also been reported in a hypercalcemic patient [37]. Usually, the hypercalcemia is mild, self-limiting, and resolves gradually after weaning [37–39].

Hypercalcemia in hypoparathyroid patients taking vitamin D in the postpartum period

Hypercalcemia may develop in hypoparathyroid patients treated with vitamin D in the postpartum period [40–43], and conversely hypocalcemia may resolve in lactating hypoparathyroid patients [44]. The hypercalcemia is associated with an increase of serum PTHrP released systematically during lactation. Mather et al. [43] determined serum PTHrP levels from the late third trimester throughout lactation in a hypoparathyroid woman taking a maintenance dose of vitamin D, and demonstrated a rapid and transient increase of PTHrP during lactation when hypercalcemia developed. Since suckling promotes the secretion of prolactin that stimulates PTHrP production in the mammary gland, suckling is considered to promote the movement of calcium from the maternal bone to the milk [1].

Pregnancy-associated hypercalcemia (humoral hypercalcemia of pregnancy)

PTHrP-associated hypercalcemia during pregnancy and in the postpartum period is usually mild, and serum level of PTHrP is slightly increased. However, we have seen a patient who developed hypercalcemic crisis after normal delivery of an infant. Extensive examination of the patient, who was admitted to the Intensive Care Unit and could not breast-feed the newborn, failed to reveal any malignant lesion.

Clinical course of the patient

A 28-year-old primigravida woman was admitted to the Maternal and Perinatal Center of Tokyo Women’s Medical University Hospital in mid March 1994. The patient’s medical and family histories were not contributory. The patient had been healthy until she became pregnant; from the mid-term period, she became anorexic and her body weight decreased. At the beginning of February 1994, she was admitted to a local hospital due to threatened miscarriage, and later became confused and stuporous. Leukocytosis, anemia, and renal dysfunction were found, and the patient was referred to our hospital (Fig. 1).

On the first hospital day, she delivered a healthy baby at the 33rd week of gestation. On the following day, marked hypercalcemia (17.9 mg/dl), hypoalbuminemia (2.1 g/dl), hyperamylasemia (431 U/L), and marked leukocytosis (24,400/mm$^3$) were found. The corrected serum level of calcium [45] was 19.4 mg/dl (Fig. 1). Infusions of saline solution and elcitonin (eel calcitonin, Asahi Kasei, Tokyo, Japan) were administered at a daily dose of 40 U twice for 4 days. To control the severe hypercalcemia, the patient was transferred to the Department of Medicine on the third postpartum day.

The patient was 163 cm tall, and weighed 46 kg. She was disoriented and stuporous, and could not respond to simple questions. The blood pressure was 190/100 mmHg, and the pulse rate was 110/min. The thyroid was normal, and the breasts were normal in size. The abdomen was flat but the patient complained of slight abdominal pain on palpation of the left upper quadrant. The turgor was normal after saline infusion. The extremities had no edema, and deep tendon reflexes were normal.

On the first day of admission, CBC revealed slight anemia (Hb 8.3 g/dl, RBC 2.81 × 10$^6$/mm$^3$, Ht 24.5%), and marked leukocytosis (46,200/mm$^3$). The serum levels of total protein, albumin, calcium, phosphate, BUN, and creatinine were 4.2 g/dl (reference range 6.5–8.5 g/dl), 1.8 g/dl (3.8–5.1 g/dl), 15.0 mg/dl (8.8–10.6 mg/dl), 5.2 mg/dl (2.5–4.3 mg/dl), 50.0 mg/dl (8–20 mg/dl), and 2.6 mg/dl (0.7–1.3 mg/dl), respectively. Serum levels of amylase and lipase were elevated to 476 U/L (135–364 U/L) and 1149 U/L (16–141 U/ml), respectively. Intact PTH was suppressed
to <5 pg/ml (23–73 pg/ml), whereas the serum level of PTHrP was markedly elevated to 28.4 pmol/L (<1.1 pmol/L) (Mitsubishi Yuka Co., Tokyo, Japan). Abdominal CT scan revealed only a slightly swollen pancreas, suggesting acute pancreatitis, but no additional abnormal lesion was found. A large amount of saline, gabexate mesilate (FOY, Ono Pharmaceutical Co., Osaka), nitroglycerin and furosemide were administered. Under a tentative diagnosis of hypercalcemic crisis accompanied by acute pancreatitis, pamidronate was administered at a dose of 45 mg on the 3rd postpartum day. Thereafter, the serum level of calcium decreased rapidly to 10.3 mg/day by the 10th postpartum day, accompanied by a decrease in the serum level of PTHrP (Fig. 1). By the 10th postpartum day, the patient’s consciousness had gradually improved. The patient denied taking any medication such as vitamin D, vitamin A, or calcium supplements. Although a paraneoplastic syndrome of hypercalcemia and leukocytosis was initially suspected [46], an extensive survey of the whole body revealed no abnormal lesion. The leukocytosis gradually disappeared, and the WBC normalized (7500/mm$^3$) by the 14th postpartum day. The patient was discharged at the beginning of May, with normalized serum levels of calcium, intact PTH and PTHrP. She has since been normocalcemic for more than 4 years.

Since the amnion in the human uteroplacental unit shows the highest expression of PTHrP mRNA and the PTHrP concentration in amniotic fluid is 20–40 pmol/L from the third trimester of pregnancy [47], we presume that PTHrP was produced abundantly in the placenta and that a large amount of it spilled into the systemic circulation, increasing PTHrP to a serum level approaching that attainable in patients with HHM [48].

Acute renal failure secondary to acute hypercalcemia is usually reversible [49]. Treatment of hypercalcemia in pregnancy is not different from that in non-pregnant women. Most importantly, dehydration should be corrected by a massive infusion of saline solution to recover GFR and increase the filtered load of calcium. To promote calcium diuresis, loop diuretics are routinely administered. As a result of these procedures, the urine volume was increased to 6 L/day, accompanied by an increase in the urinary excretion of calcium (>600 mg/day) by the 5th postpartum day (Fig. 1). Although calcitonin was slightly effective for a few days, pamidronate was administered after the delivery, and the serum level of calcium decreased rapidly to the normal range.

Clinical course of the newborn

A female child weighing 1766 g was born by spontaneous delivery in good condition with an Apgar score of 8–9. No abnormalities were noted on physical examination. As expected, the total serum calcium concentration was elevated to 14.9 mg/dl. In an attempt to prevent neonatal hypocalcemia, calcium gluconate was administered on the first neonatal day.
However, the serum calcium level subsequently remained high, and calcium infusion was discontinued from the 2nd neonatal day, the baby being supplied only with milk. The infant frequently developed apnea, and doxapram (Dopram, Kissei Pharmaceutical Co., Nagao, Japan) was administered. The serum level of calcium gradually decreased to 8.0 mg/dl on the 9th neonatal day, and thereafter increased gradually to the normal level (Fig. 1). The baby’s general condition became good and the body weight increased to 2705 g before discharge on the 51st neonatal day.

Usually, the serum level of calcium in the fetus is controlled by PTHrP secreted from the parathyroid glands and placenta [1, 18]. After delivery, PTHrP secretion from the parathyroid gland rapidly decreases and PTH gradually increases in the neonatal period [1]. Although the serum levels of PTH and PTHrP were not determined in the present newborn, it is interesting to speculate that PTHrP may have been persistently and excessively secreted from the parathyroid gland in the neonate, as the hypercalcemia persisted for several days after delivery.

Various causes of hypercalcemia

Milk alkali syndrome in pregnancy

Among rare causes of hypercalcemia [50], milk alkali syndrome is characterized by the triad of hypercalcemia, alkalosis, and renal insufficiency associated with the ingestion of a large amount of calcium and absorbable alkali. Usually the amount of calcium exceeds 3 g per day. Recently, several patients with milk alkali syndrome during pregnancy have been reported [51–56]. It is interesting that despite a marked increase in the serum level of calcium (4.12 mmol/L; reference range 2.1–2.6 mmol/L) in a boy delivered by caesarian section at 35 weeks of gestation, neonatal hypocalcemia did not occur, probably due to the short duration (only 1 month) of hypercalcemia [52]. This is in contrast to suppressed development of the fetal parathyroid glands in the neonate born to a mother with PHPT in whom prolonged hypercalcemia had been present throughout pregnancy.

Although PTHrP was reportedly not increased in some cases [52, 55], markedly elevated serum levels of PTHrP (34.9 pmol/L) have been reported in pregnant women with milk-alkali syndrome [53]. Since the level of PTHrP progressively increases during pregnancy and the postpartum period [57], excessive intake of calcium together with increased PTHrP and 1,25-(OH)_{2}D_{3} are synergistically involved in the hypercalcemia. Although the mechanism remains unknown, a transient increase of PTHrP (1.7 pmol/L) has also been noted in a non-pregnant woman with hypercalcemia due to excessive intake of calcium supplements [58].

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