A Case of a Pregnant Patient on Hemodialysis who Showed Remarkable Improvement of Severe Hyperparathyroidism by Strict Serum Phosphorus Control

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Abstract:
We encountered a pregnant hemodialysis patient with severe hyperparathyroidism (HPT). Although her disease was considered to be refractory to medical treatment, the serum intact parathyroid hormone (PTH) level remarkably improved without manifestation of hypercalcemia through only strict serum phosphorus control, mainly via intensification of dialysis. The very strong correlation between the serum phosphorus level and serum intact PTH level suggested the possibility of secondary HPT. She ultimately gave birth to a healthy baby. The clinical course of the patient’s HPT and the growth of the child have been good for more than six years.

Key words: pregnancy, hemodialysis, secondary hyperparathyroidism, intact parathyroid hormone

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Introduction

Pregnancy in women undergoing hemodialysis is very rare (1), but when it does occur, it is often accompanied by difficulty in both the mother and the infant (2).

We encountered a pregnant hemodialysis patient whose severe hyperparathyroidism (HPT) with possibly secondary involvement was remarkably improved by strict serum phosphorus control after conception and who gave birth to a healthy baby. While there have been reports regarding cases of pregnant women with primary hyperparathyroidism (PHPT) (3, 4), to our knowledge, no case of a pregnant dialysis patient with secondary hyperparathyroidism (SHPT) has been reported.

Case Report

The present patient had immunoglobulin A (IgA) nephropathy and a serum creatinine level of 1.2 mg/dL in year X-2 (10 months before dialysis initiation). She initiated maintenance hemodialysis due to rapid progression of IgA nephropathy at the previous hospital in year X-1. At the initiation of dialysis, the serum intact parathyroid hormone (PTH) level was 286 pg/mL.

In year X, she moved and was referred to our related hospital for maintenance hemodialysis at 39 years of age. At that time, she had refused all medications except for calcium channel antagonists and calcium carbonate, as she strongly wished to become pregnant. She had not shown good dietary control, demonstrating a >10% weight gain between dialysis sessions, along with hyperphosphatemia (7.5±1.2 mg/dL average serum phosphorus level before dialysis) and severe HPT (1,352±196 pg/mL average serum intact PTH level before dialysis) (Table 1)(Fig. 1).

Three months after her referral to our related hospital (19 months after dialysis initiation), she naturally became pregnant. In previous studies, it was reported that a dialysis time exceeding 20 hours and a blood urea nitrogen (BUN) level <50 mg/dL before dialysis improved outcomes of pregnant patients, such as the infant survival rate (5, 6), birth weight, and gestational age (7). Therefore, in the present case, the dialysis time was extended from 13.5 hours per week to 20 hours (5 hours/session×4 times) per week. The size of the...
Figure 1. The clinical course of chronic kidney disease-mineral and bone disorder during the perinatal period. cCa: serum calcium corrected by serum albumin, intact PTH: serum intact parathyroid hormone, P: serum phosphorus. If hypoalbuminemia occurred (<4.0 g/dL), the corrected calcium level was calculated as follows: serum calcium level (mg/dL)+[4 - serum albumin level (g/dL)]

dialysis membrane was changed from 1.8 m² to 2.1 m², and the blood flow rate was also increased from 200 mL/min to 250 mL/min (Table 1).

At the 22nd week of gestation, she was admitted to our hospital for excessive amniotic fluid. At that time, we detected two swollen parathyroid glands by ultrasonography. The size of the left upper gland and right lower gland were 18×7×5 mm and 10×8×5 mm, respectively. Inside both swollen glands, blood flow was observed (Fig. 2).

With appropriate dietary control after admission in addition to adjustment of medication and intensification of dialysis therapy, her average serum phosphorus level improved to 2.9±0.3 mg/dL, and her average serum intact PTH level also remarkably decreased to 269±136 pg/mL before dialysis (Table 1) (Fig. 1). The ratio of the serum intact PTH level/serum whole PTH level was 1.65, which was within the normal range. As a phosphate binder, only calcium carbonate, which has an established safety for pregnant women, was used in this case. In addition, alfacalcidol 0.5 μg/day was carefully prescribed with regular monitoring of the serum calcium and 1,25-dihydroxy vitamin D₃ (1,25-(OH)₂D₃) levels in order to keep the serum calcium level within the target range recommended by the Japanese Society for Dialysis Therapy (JSDT) guideline (8) and the 1,25-(OH)₂D₃ level around the lower limit of the normal range (20 pg/mL). At the 27th week of gestation, since the serum intact PTH and calcium levels had increased near the upper limit of each target range, alfacalcidol was switched to intravenous maxacalcitol 2.5 μg (3 times/week, after dialysis). She subsequently never showed hypercalcemia during pregnancy.

We scheduled a Caesarean section at the 32nd week of gestation. On the morning of the day of the operation, there

**Table 1. Dialysis Condition and Laboratory Data.**

|                      | Before pregnancy | During pregnancy |
|----------------------|------------------|------------------|
|                      | Outpatient       | Outpatient       | Admission       |
| Dialysis time (hour/week) | 12               | 20               | 20              |
| M embrane area (m²)    | 1.8              | 2.1              | 2.1             |
| Blood flow rate (mL/ min) | 200             | 250              | 200             |
| Average BUN (mg/dL)    | 69.5±8.8         | 35.1±11.4        | 24.0±2.8        |
| Average P (mg/dL)      | 7.5±1.2          | 3.2±1.5          | 2.9±0.3         |
| Average intact PTH (pg/mL) | 1352±196        | 746±249          | 269±136         |

BUN: blood urea nitrogen, P: serum phosphorus, intact PTH: intact parathyroid hormone
were no abnormalities in her vital signs, blood examination findings, or fluid volume. However, immediately after the administration of famotidine and metoclopramide just before the operation, the patient complained of dyspnea and chills. Since tongue edema was also observed, she was intubated. Subsequently, her blood pressure dropped to 70/37 mmHg, and 1 mg of adrenaline was administered. The fetal heart beat also decreased to 50 bpm. After restoring the mother's blood pressure, emergency Caesarean section was performed under general anesthesia. At birth, the newborn weighed 2374 g and showed severe asphyxia. The Apgar score was 0 points at 1 minute and 0 points at 5 minutes. The newborn's heartbeat was restored 8 minutes after birth by ventilator management and intravenous administration of adrenaline 0.4 mg. Both the mother and newborn subsequently recovered steadily and left the ventilator several days later. Both were discharged 14 days after giving birth without any apparent residual disability.

Since her discharge, the patient has been undergoing maintenance hemodialysis at a nearby clinic for more than six years. The clinical course of HPT of the patient has been good and stable with medication, including sevelamer hydrochloride, lanthanum carbonate, and cinacalcet, which were added after giving birth (Table 2). However, the size of her parathyroid glands has not yet shrunk. The longest diameters of the largest gland were 18 mm, 20 mm, and 20 mm during pregnancy, at 3 months after giving birth, and 6 years later, respectively (Table 2) (Fig. 2). The bone mineral density was 110% of the young adult mean (YAM) in the lumbar spine and 83% of the YAM in the femoral neck at 6 months after giving birth. The growth of the child has been good, with no obvious abnormalities observed (Table 3).

### Discussion

We encountered a pregnant hemodialysis patient whose severe HPT was remarkably improved by strict serum phosphorus control after conception and who gave birth to a healthy baby. In previous reports, the pregnancy rate of chronic hemodialysis patients was as low as 0.7% yearly (1), and the infant survival rate was only 40.2% even if patients managed to become pregnant (2). To our knowledge, no case of a pregnant dialysis patient with SHPT has yet been reported, although there have been some reports of cases of pregnant women with PHPT (3, 4).

According to a nationwide questionnaire survey in Japan performed in 1996, the dialysis vintage among pregnant dialysis patients ranges widely from 0.6 to 25 years (average 8.0±5.6 years) (9). A review article regarding pregnancy in chronic dialysis patients indicated that the group with surviving infants had a significantly shorter dialysis vintage (37 cases, 29±25 months) than the group with infant deaths (15 cases, 52±49 months) (p=0.036) (10). However, in the other report, there was no statistically significant difference in the dialysis vintage between the group with surviving infants and the group with infant deaths, although the dialysis vintage in the group with surviving infants (18 cases, 3.6±4.1 years) tended to be shorter than in the group with infant deaths.
do not have hypercalcemia has been unclear. PHPT is more likely to induce hypercalcemia than SHPT due to kidney failure. Because activated vitamin D is suppressed in chronic hemodialysis patients, bone becomes resistant to PTH, and the serum calcium level is corrected by hemodialysis. In the present case, the patient had fortunately never shown hypercalcemia thanks to very careful and strict adjustment of her vitamin D receptor activators and the use of low-calcium di-

dalyrate.

However, in chronic dialysis patients with severe SHPT refractory to medication, parathyroidec-
tomy (PTx) is recommended (8). In the present case, the parathyroid glands were suspected of showing nodular hyperplasia and were refractory to medication because the serum intact PTH level exceeded 500 pg/mL, the diameter of the largest gland exceeded 1 cm, and its estimated volume exceeded 500 mm³ (8) (Table 2) (Fig. 2). However, due to concerns that the large fluctuation in the serum calcium level after PTx might adversely affect the fetus, we decided not to perform surgery during pregnancy in the present case. Through strict serum phosphorus control, including appropriate dietary control, careful medication, and intensification of dialysis therapy, the serum intact PTH level markedly decreased to almost the target range (8), and she ultimately gave birth to a healthy baby.

We initially considered scheduling PTx after the delivery. However, she developed shock due to a drug allergy just before the scheduled Caesarean section. Since then, she has not wanted to undergo any operation and has therefore been treated only with the usual dialysis therapy and medication, including phosphate binders, vitamin D receptor activators, and cinacalcet. Fortunately, her serum phosphorus, calcium, and intact PTH levels have been maintained almost within the target ranges set by the JSDT guideline (8) for more than six years. The shock before the Caesarean section was considered to be a case of maternal anaphylactic shock in

Table 2. Long-term Clinical Course of Chronic Kidney Disease-mineral and Bone Disorder.

|                        | During | After delivery |
|------------------------|--------|---------------|
|                        | pregnancy | 3 months | 3 years | 5 years | 6 years |
| S- cCa (mg/dL)        | 9.9     | 8.9      | 10.0   | 9.1     |
| S- P (mg/dL)          | See Figure 1. | 5.0     | 4.8     | 4.3     | 4.4     |
| S- intact PTH (pg/mL) | 144     | 240      | 291    | 230     |
| Calcium carbonate     | 3,000   | 1,500    | 1,500  | 3,000   | 3,000   |
| Sevelamer hydrochloride | (mg/day) | 750     |         |         |         |
| Lanthanum carbonate   | 25      | 50       | 50     | 75      |
| Cinacalcet (mg/day)   | 10×7    | 10×7     | 13×8   | 16×7    | 10×8    |

Table 3. Laboratory Data of the Child.

|                        | At birth | 5 months |
|------------------------|----------|----------|
| S- cCa (mg/dL)        | 10.6     | 10.2     |
| S- P (mg/dL)          | 7.4      | 6.8      |
| S- ALP (IU/L)         | 717      | 850      |
| S- intact PTH (pg/mL) | 5        | 19       |

S-cCa: serum calcium corrected by serum albumin, S-P: serum phosphorus, S-intact PTH: serum intact parathyroid hormone
If there was hypoalbuminemia (<4.0 g/dL), corrected calcium level was calculated as follows.
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In cases of pregnant women with PHPT presenting with hypercalcemia, it has been recommended that the parathyroid glands be surgically removed by the second trimester in order to avoid a risk of miscarriage, stillbirth, intrauterine fetal growth retardation, and newborn tetany (3, 4). In case of maternal hypercalcemia, the risk of newborn tetany through fetal PTH suppression is of concern. However, as PTH itself does not transfer to the placenta (11), the optimum treatment strategy of pregnant patients with HPT who

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response to either famotidine or metoclopramide, which were used as preoperative medications. The patient had a history of allergy to methyldopa hydrate and heparin-induced thrombocytopenia. When a new drug is administered to the patient, sufficient attention should be paid to the likelihood of a drug allergy. There were no abnormalities in the blood pressure, fluid volume, or blood chemistry findings, including electrolytes, before the shock occurred, so the shock was not considered to have been related to kidney failure.

Very few data are available on the safety of medication for CKD-MBD (chronic kidney disease-mineral and bone disorder) in pregnant dialysis patients. We prescribed calcium carbonate as a phosphate binder for the patient because it has been used in pregnant dialysis patients safely. Since sevelamer hydrochloride, lanthanum carbonate, and cinacalcet lacked information on their safety in pregnant women, those three drugs were not administered during pregnancy in the present case. Although some animal studies have suggested the potential for dose-dependent fetal toxicities of vitamin D, there have been no published reports on its teratogenic effects in humans, and animal and human studies have shown that fetal excess of vitamin D metabolites are unlikely to occur when maternal concentrations are within normal ranges (12, 13). Regarding maxacalcitol, studies of pregnant rats indicated that the dose with no effect on fetal development during the organogenesis period was 100 μg/kg/day, which is markedly higher than the regular dose (14).

Why such severe HPT was remarkably improved with only conservative treatment is unclear, but we propose the following potential reasons: 1) In the present case, the duration of chronic kidney failure before the initiation of dialysis was very short, at most 10 months, because of the rapid progression of IgA nephropathy. In addition, the duration between dialysis initiation and pregnancy was also short (19 months); 2) At the initiation of dialysis, since she had refused most medications and her dietary control had been very poor, the serum phosphorus level had been extremely high, occasionally exceeding 9 mg/dL; and 3) However, after conception, frequent and long dialysis sessions and good dietary control exceedingly improved her hyperphosphatemia and uremia, with the effects further emphasized during admission because of even better dietary control.

Although no similar reports have been found so far, the extremely rapid improvement in her serum phosphorus level and the status of uremic toxins is similar to the changes before and after kidney transplantation (KT). Indeed, in the present case, the average BUN level before dialysis decreased from 69.5±8.8 mg/dL before pregnancy to 24.0±2.8 mg/dL during admission, and the average serum phosphorus level before dialysis decreased from 7.5±1.2 mg/dL before pregnancy to 2.9±0.3 mg/dL during admission (Table 1). Along with changes in the serum phosphorus levels, the serum intact PTH levels dropped rapidly, with both values very strongly correlated (Fig. 1). Such remarkable changes are unlikely to occur in typical maintenance dialysis cases. However, there have been many cases in which severe SHPT was remarkably improved after KT (15). For example, Bravo et al. reported a case in which the serum PTH level dropped from 1,233 pg/mL to 70 pg/mL and the total volume of the parathyroid glands decreased from 1,412 mm³ to 510 mm³ (15). They mentioned that KT might inhibit or reduce the effects of those factors underlying uremic parathyroid hyperplasia, such as the decreased expression of calcium-sensing receptors and vitamin D receptors in parathyroid tissue, and that after successful KT, parathyroid cells might show a decreased rate of proliferation and a maintained or even increased rate of apoptosis (15). Evenepoel et al. reported that the duration of dialysis treatment was related to persistent HPT after KT (16). We considered that the short duration of kidney failure before pregnancy, as well as the extreme reduction in her serum phosphorus level and uremic toxin after recognition of pregnancy, which was similar to the changes observed after KT, enabled the remarkable improvement of such severe HPT.

After giving birth, while the dialysis time, size of the dialysis membrane, and blood flow rate were reverted to the same values as before pregnancy, her serum phosphorus, calcium, and intact PTH levels were maintained at nearly within the target ranges for more than six years with the addition of sevelamer hydrochloride, lanthanum carbonate, and cinacalcet. Recently, with the introduction of calcimimetics in cases of severe SHPT, which had been considered resistant to conventional medication, the numbers of such cases showing a good clinical course without PTx have been increasing, as was observed in the present case. However, our patient’s parathyroid glands have not yet shrunk significantly (Table 2), so further observation of the bone mineral density and cardiovascular calcification is needed.

The authors state that they have no Conflict of Interest (COI).

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