Primary Hyperparathyroidism and Pregnancy: A Case Report
Primer Hiperparatiroidizm ve Gebelik: Vaka Bildirimi

Süheyla Görar, Gönül Koç, Ziynet Üç, Dilek Dellal, Zehra Candan, Cavit Çulha, Yalçın Aral
SB. Ankara Eğitim ve Araştırma Hastanesi, Endokrinoloji ve Metabolizma Hastalıkları Kliniği, Ankara, Türkiye

Abstract
Abstract Primary hyperparathyroidism (PHP), more common in women, is a disease associated with high calcium levels. Pregnancy within PHP is a condition of life in terms of both maternal and fetal facts. We’ve reported our patients who came to us with urinary symptoms with hypercalcemia, she was diagnosed as PHP. Surgery was recommended to her but she was not operated. Meantime, patient was pregnant. During her pregnancy, parathyroidectomy was applied at 2 trimester. After parathyroidectomy, preeclampsia was diagnosed. During the follow-up, fetus died of intrauterine death. Her preeclampsia declined, after fetus extraction. By this issue, we wanted to draw attention to complications of PHP throughout pregnancy problems. Turk Jem 2011; 15: 16-9

Key words: Primary hyperparathyroidism, pregnancy

Özet

Anahtar kelimeler: Primer hiperparatiroidizm, gebelik

Introduction
Primary hyperparathyroidism (PHP) results from excess parathormone (PTH) secretion and is characterized by overt hypercalcemia. PHP is diagnosed approximately 100,000 new cases per year in the United States (1). Only three studies have been published on the community-based prevalence and incidence of PHP in the last 10 years. First publication reported a population-based incidence rate of PHP of 21.6 per 100,000 person-years between 1993 and 2001 in the USA. Second, in Norway, PHP prevalence in the population <76 years was estimated at 0.17% in men and 0.45% in women in a study from the 1990s. Finally, in Sweden, a PHP prevalence of 21.6 per 100,000 person-years between 1993 and 2001 in the USA. Second, in Norway, PHP prevalence in the population <76 years was estimated at 0.17% in men and 0.45% in women in a study from the 1990s. Finally, in Sweden, a PHP prevalence of 2.1% was observed in women aged 55–75 years in the early 1990s. Another study from Switzerland was reported mean annual hospitalisation rate of patients with PHP of 8.3/100.000 inhabitants, and an in-hospital prevalence of PHP of 43.8/100.000 hospitalisations, from 2000 to 2004 (2). PHP is two to three times more common in women than men. The incidence of PHP in women of child-bearing age is estimated to be approximately eight cases per 100,000 population (3). PHP is caused by solitary parathyroid adenomas (approximately 85%). While a single adenoma is found in most cases, multiple parathyroid adenomas (4%) and diffuse hyperplasia (10%) have been reported in cases (4). Hypercalcemia during pregnancy is rare. It is usually secondary to primary hyperparathyroidism. It causes significant fetal and maternal morbidity if it remains unrecognized and untreated (5). We’ve reported the follow-up problems of a pregnant woman patient who was diagnosed as PHP.
Case Report

A 39 year-old woman was approved at the urology clinic of Ankara Research and Training Hospital because of recurrent urinary tract infections with renal stone on the bilateral urinary tract and kidneys. The woman was evaluated by an urologist. The ultrasonographic examination showed the left kidney atrophic filled the pelvicicalceal stones and right kidney is as seen as hypertrophic with pelvicicalceal eclusia and milimetric stones. Right ureterolithotripsy and right double-J (DJ) stent on right ureter was performed by urology clinic. At the same time, serum calcium of 14.7 mg/dl (8.2-10.2 mg/dl) and PTH levels were elevated; 313 pg/ml (15-88 pg/ml). Therefore, she was consulted to our endocrinology clinic and other diagnostic laboratory tests were recommended. Blood sample of the patient was measured serum calcium of 12.1 mg/dl, phosphorus 2.8 mg/dl, creatinine 1.8 g/dl. Glomerular filtration rate was estimated 33 ml/min. Neck ultrasonography revealed at 11x11 mm nodular lesion at the left parathyroid region. Her thyroid and parathyroid sintigraphy was showed parathyroid adenoma at inferior of left thyroid region. The patient was diagnosed as PHP. She was referred to general surgery clinic for parathyroiodectomy but she didn't come to her follow up.

Three months later she came again with complaint of nausea, vomiting, loss of weight. The patient was rehospitalized to reevaluate. The laboratory examinations were repeated since the history of PHP were known. Patient was found to be 13 th week of gestation (WG) unexpectedly. After fluid replacement with forced diuresis she were stabilized but her calcium levels didn't change. Due to persistence of significant hypercalcemia poorly responsive to diuretic and fluid replacement therapy she was transferred to general surgery clinic. Parathyroidectomy was performed in the 14th WG. Right and left parathyroid adenoma were excised in neck exploration. The histologic exam of the removal mass was parathyroid adenoma, in both. After operation her calcium and PTH levels decreased. Blood work showed a serum calcium 10.2 mg/dl and PTH levels 70.4 pg/ml. In the following days she didn't need oral or intravenous calcium replacement. Fetal ultrasonography performed after surgery, showed a living fetus. The patient was discharged one week after operation.

At 26 WG, a new hospitalization was required for the presentation of renal function deficiency, proteinuria, hypertention and right kidney hydronephrosis. Then she was hospitalized urology clinic for renal DJ cataterization. Right ureteroscopy and DJ stent was performed and the patient was discharged. The laboratory data of the patient before, during and after pregnancy are shown in Table 1.

Her follow up is still continued by urology and nephrology clinics. She hasn't any symptom like weakness, polyuria, irritability, loss of weight associated with hypercalcemia.

Discussion

Hypercalcemia during pregnancy is uncommon. The presence of hypercalcemia in a case necessitates the differential diagnosis. Hypercalcemia is mostly associated with PHP. Because up to 80% gravid patients with PHP are asymptomatic, diagnosis is more difficult. Furthermore, humoral hypercalcemia may also develop due to PTH-related protein. This condition is physiologically excessive production of PTHrP in placenta and/or mammary gland in pregnancy, puerperium, lactation) or milk-alkali syndrome (associated with intake of a large amount calcium and absorbable alkali) or malignant tumors (3).

PHP cases which remains unrecognized during silent phase and then become overt, mostly gastrointestinal, muskuloskeletal and urinary systems are effected. Complications associated with PHP in pregnancy have been reported to occur in up to 67% of mothers and 80% of fetuses. The most maternal complications are nephrolitiasis (24-36%), bone disease (13-19%), pancreatitis (7-13%). Hyperemesis gravidarum, preeclampsia, urinary tract infections, muscle weakness, mental status changes can be seen (6). There are elevated miscarriage rate. In .class of one a study result, it's been emphasized that the miscarriage rates are 3 or 4 times more in PHP pregnant (7). Thus, the early diagnosis of PHP if possible before pregnancy and then surgical treatment is important. Hypercalcemic crisis is one of the most feared complication (6).

Reported fetal complications include intrauterine growth retardation, preterm delivery, intrauterin fetal demise, postpartum neonatal tetany. A four-fold decrease in perinatal complications may be achieved with appropriate therapy (6).

<table>
<thead>
<tr>
<th>Laboratory test (Normal range)</th>
<th>Before pregnancy</th>
<th>Pregnancy 13 WG preoperation</th>
<th>Pregnancy 15 WG postoperation</th>
<th>Pregnancy 24 WG delivery</th>
<th>After pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (8.2-10.2 mg/dl)</td>
<td>12.1</td>
<td>13.7</td>
<td>10.9</td>
<td>10.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Phosphorus (2.5-4.5 mg/dl)</td>
<td>2.8</td>
<td>2.4</td>
<td>2.9</td>
<td>3.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Magnesium (0.77-1.03 mmol/l)</td>
<td>1.0</td>
<td>0.6</td>
<td>0.6</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Potassium (3.5-5 mmol/l)</td>
<td>3.9</td>
<td>3.6</td>
<td>3.6</td>
<td>3.9</td>
<td>3.7</td>
</tr>
<tr>
<td>PTH (15-88 pg/ml)</td>
<td>313</td>
<td>422.6</td>
<td>78.8</td>
<td>73.3</td>
<td>70.8</td>
</tr>
<tr>
<td>Creatinine (0.81-1.2 mg/dl)</td>
<td>1.8</td>
<td>1.4</td>
<td>1.3</td>
<td>2.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Albumine (3.5-5.2 g/dl)</td>
<td>3.1</td>
<td>3.7</td>
<td>3.4</td>
<td>3.3</td>
<td>3.7</td>
</tr>
</tbody>
</table>
The continuity of hypercalcemia and hypercalciuria in a PHP can lead to kidney stones, nephrocalcinosis, polypria, polydipsia and uremia with the loss of renal functions is unavoidable. Renal functioning is progressively affected with delayed or non-treated PHP diagnostic. An ultrasonographic findings of a retrospective study showed that in PHP and a control group of patients, asymptomatic renal stones of PHP patients were seen four times more (1). It’s known that PHP has an increasing risk of death. Factors increasing this risk are shown as spoil of renal functioning, glomerular filtration rate and the capacity of renal tubuler concentration. In conclusion, renal impairment in hyperparathyroidism is thought to become due to other mechanisms except from renal stone formation (8). Other cause of elevated parathyroid hormone may be secondary complication of chronic renal insufficiency and end-stage renal disease. Although its exact pathogenesis is unknown, hyperphosphatemia, hypocalcemia, decreased expression of calcium and vitamin D receptors, and parathyroid hormone resistance may each play a part (9). In our case, we considered renal function impairment from kidney stones of PHP because of hypophosphatemia, hypercalcemia and pathological double parathyroid adenomas. Hypercalcemia during the pregnancy is a life threatening condition for both mother and fetus. After the confirmation of PHP with maternal imaging methods USG or CT or MRI in a pregnant patient who has hypercalcemia and the elevation of PTH, follow up is crucial (6). If asymptomatic moderate hypercalcemia (<12 mg/dl) is present, it is appropriate to follow a conservative policy. Oral hydration and decrement of dietary calcium intake with are recommended. The patient can be followed up to the end of first trimester as long as calcium level is kept below 12 mg/dl (10). A symptomatic woman with serum calcium level greater than 12 mg/dl needs close cardiac monitorization. Beside adequate hydration and diuresis, calcitomin or biphosphonates are the other medical treatment options. Emergent parathyroidectomy should be considered if the clinical stabilization and control of hypercalcemia can not be accomplished. Parathyroidectomy is recommended during the second trimester when the risk of anesthesia-induced preterm delivery is lowest and organogenesis is complete (4, 11). Surgery during the third trimester classically has a higher risk of preterm labor. Carella and Gossain reviewed 38 women who underwent parathyroidectomy 7 women during first trimester, 18 during second, and 12 during third trimester. A 58% perinatal complication rate was reported after third trimester parathyroidectomy (11). At the same time cases of uncomplicated third trimester have been increasingly reported (12). The strategy of surgical treatment depends on the ability to localize the parathyroid glands. The minimally invasive surgery or bilateral neck exploration can be preferred (13,14). In our case blood calcium level is greater than 12 mg/dl despite medical treatment therapy. Parathyroidectomy was performed during second trimester, and two parathyroid adenomas were excised. Mostly a single adenoma is responsible for PHP. Presence of multiple adenomas are rare (4%). In this respect, our case is interesting. There are cases of double adenoma with PHP detected during pregnancy and after surgery (15).

One of the most important complications which affect both mother and the fetus is preeclampsia. It affects 5% of all pregnancies. The mainstay of this diagnosis is a combination of new-onset hypertension and proteinuria. Diminished renal plasma flow, decrease glomerular filtration rate, and proteinuria constitute the key renal manifestations of preeclampsia (16). Risk factors for preeclampsia include socio-demographical factors, genetic factors, pregnancy factors. Besides, in the medical history of pregnant, there’s also obesity, chronic hypertension, diabetes mellitus and chronic renal disease (17). In addition to all these factors, there are some reports suggesting that the disorders of calcium metabolism and primary hyperparathyroidism may be responsible from preeclampsia which is an important issue during the course of pregnancy (12,18). In our case, it is thought that preeclampsia was result from chronic renal failure despite normocalcemia was gravidated during third trimester. In our patient, the left kidney was filled with renal stones which reduced its functioning severely and in the right kidney, there were also compensatris hypertrophy and renal stones. Although there was a severely affected renal functioning secondarily developed to PHP, having no surgical treatment downturned our patient clinically bad. The unexpected pregnancy of the patient also stressed both herself and the fetus. The parathyroidectomy operation had to be done during her pregnancy. Even though no problems occured after surgery according to mother and fetus health, it’s for sure that operation is a source of stress for both mother and fetus. The preeclampsia diagnosis which is thought to have played an important role in urological problems and reduction of renal functioning in advanced stages of pregnancy, has started a new difficult challenge for fetus and the mother. The fetus was lost in this process. If our case has been operated as soon as she was diagnosed as PHP and her renal functioning was taken under control, probably, she would have a healthier pregnancy process with no stress and therefore no unintended consequences would occur. In this respect, the recognition and treatment of PHP in women of childbearing age needs a more important and careful attention.

Conclusion

The existence of PHP during gestation carries vital risks for mother and fetus. Parathyroidectomy is the preferred method for symptomatic hypercalcemia at the second trimester. Co-occurrence of hyperparathyroidism and pregnancy is the troublesome process which needs careful fetal and maternal monitorization and follow up before and after surgery.

References