A Case of Pregnancy Complicated by Primary Hyperparathyroidism Due to a Parathyroid Adenoma

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Conflict of interest: None declared

Patient: Female, 28
Final Diagnosis: Primary hyperparathyroidism
Symptoms: Clavate swelling of the tubular bones • deformation of ribs and pelvic bones • duck gait • gait disturbance • general weakness • joint restrictions • keeled thorax • lameness • muscle weakness • pain in the bones and joints • rachiocampsis
Medication: —
Clinical Procedure: C-section in the lower uterine segment by transverse incision • a thoracoscopic removal of ectopic formation of the parathyroid gland
Specialty: Obstetrics and Gynecology

Objective: Rare co-existence of disease or pathology
Background: Primary hyperparathyroidism is most common in women during the menopause and its occurrence in pregnant women is rare. However, because neonatal mortality is associated with maternal hyperparathyroidism, early diagnosis is essential. This report describes the case of a late diagnosis of primary hyperparathyroidism in a 28-year-old pregnant woman and describes the effects on the mother and neonate.

Case Report: During her second pregnancy, a 28-year-old woman presented with symptoms of general weakness, bone and joint pain, multiple fractures with bone deformity, muscle weakness, and gait disturbance. Due to the high risk of perinatal pathology, a cesarean section was performed. Several weeks later, she underwent thoracoscopic removal of an ectopic parathyroid gland located at the aortic arch. Hypocalcemia in the newborn infant required treatment with calcium and magnesium supplements.

Conclusions: This case demonstrates that primary hyperparathyroidism during pregnancy requires timely diagnosis and treatment to reduce potential maternal and fetal complications. Screening for primary hyperparathyroidism should be undertaken in pregnant women with any symptoms associated with hypercalcemia. Treatment should be individualized and includes conservative management, parathyroidectomy in the second trimester, or parathyroidectomy performed in the early postpartum period.

MeSH Keywords: Hypercalcemia • Hyperparathyroidism, Primary • Osteoporosis • Parathyroid Hormone • Pregnancy

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Background

Worldwide, primary hyperparathyroidism is the third most common endocrine disorder, after diabetes and thyroid disease, and women are twice as likely to be affected as men. In 2013, a study on the epidemiology of primary hyperparathyroidism in a racially mixed population of 3.5 million people in California reported the incidence as 4.7 per 100,000 in the age group between 20–29 years, and as 6.2 per 100,000 for the age between 30–39 years in woman [1].

Primary hyperparathyroidism is characterized by elevated serum calcium, low serum phosphorus with high parathyroid hormone (PTH) with hypercalciuria, based on the urine calcium clearance to creatinine clearance ratio. Primary hyperparathyroidism during pregnancy is usually associated with the presence of a parathyroid adenoma, which is present in approximately 80% of all cases, followed by parathyroid hyperplasia in 15% of cases, multiple adenomas in 3% of cases, and parathyroid carcinoma in 1% of cases [2].

Primary hyperparathyroidism during pregnancy occurs rarely and is often misdiagnosed or undiagnosed as between 23–80% of patients with primary hyperparathyroidism are asymptomatic [3]. During pregnancy, physiological changes that may affect and lower calcium levels include hypoalbuminemia, calcium transport across the placenta, and an increased glomerular filtration rate [4]. Also, estrogens inhibit parathyroid hormone-mediated bone resorption [5]. Symptoms associated with hypercalcemia often vary, and this can lead to a delay in diagnosis during pregnancy. The most common symptoms in women are nephrolithiasis, hyperemesis, pancreatitis or hypercalcemic crisis. Maternal complications are reported in 67% of patients, and fetal complications occur in up to 80% of cases [6,7]. The most common consequence of maternal hyperparathyroidism during pregnancy is a development of neonatal hypocalcemia, which if untreated can affect fetal development and may cause fetal or neonatal death [8].

Early diagnosis of primary hyperparathyroidism followed by appropriate management reduces these complications significantly. The optimal management of primary hyperparathyroidism during pregnancy needs to be individualized and should be based on the clinical course, gestational age, the severity of hypercalcemia and the risk to benefit assessment for each treatment option for the mother and a child. Most clinical studies and guidelines recommend parathyroidectomy as the treatment of choice for primary hyperparathyroidism occurring in pregnancy [2,9,10]. The efficacy and safety of medical treatment for primary hyperparathyroidism in pregnancy remain unknown. Conservative treatment might be used but only in primary hyperparathyroidism with mildly elevated calcium levels (≤11 mg/dL) [9]. Intravenous or oral rehydration, with or without forced diuresis with a loop diuretic, is the a first-line treatment, that has limited efficacy [9]. Few drugs are available for the management of primary hyperparathyroidism during pregnancy. In particular, the use of subcutaneous calcitonin has a pregnancy category C rating (fetal risk not ruled out due to fetal abnormalities in animal studies alone) and calcitonin does not cross the placenta but has limited efficacy due to tachyphylaxis [11]. The calcimimetic drug, cinacalcet, has also been used in combination with calcitonin and has demonstrated an effective reduction in PTH levels, but also has a category C rating and crosses the placenta [12]. Bisphosphonates cross the placenta and are toxic to the fetus at high doses, and although they have been used during pregnancy in several cases, they are not recommended [13].

This report describes the case of a late diagnosis of primary hyperparathyroidism in a 28-year-old pregnant woman and describes the effects on the mother and neonate.

Case Report

A 28-year-old woman was admitted to Endocrinology Research Center on the 9th day after her cesarean section with general weakness, pain in the bones and joints, muscle weakness, and gait disturbance. She did not smoke or drink. She had physical deformities of the thorax, ribs and pelvic bones, swelling of the tubular bones, joint restriction, an abnormal gait, and lameness were recorded at physical examination. She had a body mass index (BMI) of 20 kg/m² (Figure 1A). A bilateral costovertebral angle tenderness test was negative.

In her past medical history, she had suffered from bone pain since the age of 24 years and had her first pregnancy at the age of 25 years. At that time, she had a gait abnormality, bone pain, and muscle weakness, with bone hyperplasia on the left side of the upper jaw, which was assumed to be a neoplasm. Her first pregnancy ended at term, and the infant’s weight was 3300 g. According to the patient, the newborn was clinically healthy and did not suffer from seizures, but calcium levels were not measured. In the postpartum period, the patient underwent surgical removal of the mass in her upper jaw, but the histology and diagnosis of this was unknown. Within a year, at the age of 26 years, the patient was re-examined at her local hospital and for multiple areas of bone hyperplasia and minor traumatic fractures of fingers, ribs and pelvic bones were found and a diagnosis of fibrous dysplasia was made. There were no previous investigations into her calcium and phosphorus levels, but she received treatment with calcium supplements, which worsened her condition, resulting in weight loss of 30 kg with polyuria and polydipsia. The second pregnancy occurred four years later. She had no family history of multiple endocrine neoplasia type 1 (MEN1), MEN2 or isolated primary hyperparathyroidism.
During this second pregnancy, the patient had threatened miscarriages in the first and second trimesters. In the third trimester, the edema of lower extremities and pain in the joints were observed under the threat of premature birth. On admission to The National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow at 37 weeks gestation her laboratory tests showed severe hypercalcemia with a total calcium of 3.53 mmol/L (normal range, 2.15–2.55 mmol/L), and a phosphorus level of 0.58 mmol/L (normal range, 0.87–1.45 mmol/L), total protein of 63.1 g/L (normal range, 64–83 g/L), an elevated parathyroid hormone (PTH) level of 1,565 pg/mL (normal range, 15–65 pg/mL). Due to the high risk of perinatal pathology, severe pelvic bone pathology and development of moderate pre-eclampsia the infant was delivered urgently at 37 weeks by cesarean section with a transverse incision in the lower uterine segment. A live mature male infant was born weighing 2,917 g, length of 51 cm, and an Apgar score of 8/9. After delivery, the patient received intravenous rehydration, oxytocin, and analgesic therapy. On the 9th day after her cesarean section, the patient was referred to the Neuroendocrinology and Bone Disease Department of the Endocrinology Research Center, Moscow.

During the current hospital admission, further laboratory tests confirmed the severity of her primary hyperparathyroidism and included a PTH level of 1,515.0 pg/mL (normal range, 15–65 pg/mL), an ionized calcium level of 1.57 mmol/L (normal range, 1.03–1.29 mmol/L), total calcium level of 3.37 mmol/L (normal range, 2.15–2.55 mmol/L), a phosphorus level of 0.70 mmol/L (normal range, 0.87–1.45 mmol/L). Severe hypercalciuria and vitamin D deficiency were present. The laboratory test results are summarized in Table 1. Post-partum follow-up imagining examinations showed the typical signs of hyperparathyroid osteodystrophy and included subperiosteal resorption of the fingers and toes, numerous fractures of the fingers and toes (Figure 2), compression of vertebrae T8–T10 (Figure 1B), L2–L4 and L5 (Figure 1C). Based on the results of X-ray densitometry of the skeleton, pronounced osteoporosis of the lumbar spine and proximal femur were present with the predominant lesions of the distal forearm, which is pathognomonic for primary hyperparathyroidism. Considering the young age of the patient, X-ray densitometry measurements of bone mineral density (BMD) included the Z score (osteoporosis <–2) and showed Z-scores in L2–L4 of –3.1 SD, in the proximal part of the femur of –3.9 SD, and in the radius of –7.4 SD.

Because of the young age of the patient and the confirmed diagnosis of primary hyperparathyroidism, additional tests were performed that included insulin-like growth factor 1 (IGF-1) of 57.9 ng/mL (normal range, 150–400 ng/mL), prolactin (PRL) of...
430 U/L (normal range, 90–540 U/L), and a calcitonin level of 1.9 pg/mL (normal, <10 pg/mL). Computed tomography (CT) imaging of the abdominal and retroperitoneal space showed nephrocalcinosis and renal microlithiasis.

Scintigraphy of the parathyroid glands with technetium-99m-labeled methoxy isobutyl isonitrile (99mTc-MIBI) showed a hyperintense imaging focus in the anterior mediastinum, with abnormal foci in the skull, along the upper-lateral edge of the left orbit, the lower-lateral side of the right orbit, and cystic changes in the bones of the skull, which characterized the presence of severe hyperparathyroid osteodystrophy. According to the contrast-enhanced CT results a solitary adenoma of the parathyroid gland, measuring 8.1×22.5×33.1 mm, was seen in the bed of the thymus gland, posterior to the sternum (Figure 3). Surgical excision of the ectopic parathyroid gland adenoma was planned, but due to the patient’s hypercalcemia, and during preparation for surgery, infusion therapy with 0.9% NaCl solution was administered. The patient was also treated pre-operatively for a urinary tract infection.

### Table 1. A case of pregnancy complicated by primary hyperparathyroidism: Laboratory test results before and six months after parathyroidectomy.

| Laboratory test            | Before parathyroidectomy | Six months after parathyroidectomy | Normal values |
|----------------------------|--------------------------|------------------------------------|---------------|
| PTH (pg/mL)                | 1515.0                   | 23.7                               | 15–65         |
| Osteocalcin (ng/mL)        | 300.0                    | 171.0                              | 11–43         |
| beta-CTx (ng/mL)           | 2.46                     | 1.19                               | 0.01–0.69     |
| Alkaline phosphatase (U/L) | 2879.9                   | 543.9                              | 0–270         |
| Total calcium (mmol/L)     | 3.37                     | 2.50                               | 2.15–2.55     |
| Ionized calcium (mmol/L)   | 1.57                     | 1.14                               | 1.03–1.29     |
| Phosphorus (mmol/L)        | 0.70                     | 1.01                               | 0.87–1.45     |
| GFR (mL/min.)              | 130                      | 114                                | 90–150        |
| Calciuria (mmol/day)       | >10                      | Not measured                       | 2.5–7.5       |
| 25-OH-vitamin D (ng/ml)    | 17.6                     | 67.2                               | 30–150        |

PTH – parathyroid hormone; GFR – glomerular filtration rate; Beta-CTx or Urine BETA CrossLaps® is a marker of degraded type I collagen and of bone resorption.

**Figure 2.** A case of pregnancy complicated by primary hyperparathyroidism: Macroscopic and X-ray images of the wrist and hands. 
(A) The deformed image of the wrist and fingers of the hand. (B) X-ray image of the deformed distal tubular bones, showing acro-osteolysis, or subperiosteal resorption of the distal phalanges.
Thoracoscopic removal of the ectopic parathyroid adenoma, which was encapsulated and located near the aortic arch was performed. The adenoma measured 4.5×2.0×3.0 cm with whitish, brown and dark purple areas. The histopathology showed a benign, predominantly chief cell adenoma and a fragment of thymus tissue was identified in the excised specimen. The basal level of PTH was 1,262 pg/mL, within 15 min after the parathyroid adenoma was removed the PTH level decreased to 102.2 pg/mL. The postoperative period was uneventful.

Three days after surgery, despite the postoperative treatment with calcium (2,000 mg/day) and alfalcaldiol (2 μg/day) supplements, signs of postoperative hypocalcemia developed, which were consistent with suppressed parathyroid hormone (PTH) levels, which follows parathyroidectomy in patients with severe primary hyperparathyroidism, sometimes referred to as hungry bone syndrome (HBS), which was associated with low levels of ionized calcium of 0.98 mmol/L (normal range, 1.03–1.29 mmol/L) and total calcium of 2.0 mmol/L (normal range, 2.15–2.55 mmol/L). Hypocalcemia was successfully treated with parenteral administration of calcium supplements, including calcium gluconate 80 ml per 150 ml of 0.9% NaCl daily, and with the active metabolite of vitamin D (alfalcaldiol) at a dose of 3 μg/day. Because of the severe hypocalcemia, anti-osteoporotic therapy was not given. The patient discharged from the hospital with recommendations to continue treatment with calcium (2,000 mg/day) and alfalcaldiol (2 μg/day) supplements, with regular monitoring of her calcium and phosphorus metabolism parameters.

Three months after surgery, the patient fell and had a minor traumatic fracture of the middle third of the left femur treated by skeletal traction and a hip plaster cast. Six months after surgery, the patient readmitted to the Endocrinology Research Center for re-examination. At the time of hospitalization, the patient reported significant overall improvement, an absence of pain, increase in body weight (10 kg in six months), less muscle weakness and reduced bone hyperplasia. Laboratory test results confirmed remission of her primary hyperparathyroidism (PTH 23.7 ng/mL) and she had maintained normocalcemia (ionized calcium 1.14 mmol/L) on calcium and active metabolites of vitamin D supplements (Table 1). According to X-ray densitometry of the skeleton measured at the 33% radius osteoporosis was confirmed with a Z-score of –4.1 SD, with positive dynamics of 125% in the proximal part of the femur (Z-score –1.5 SD). Despite the pronounced positive dynamics of bone mineral density in all parts of the skeleton, high risk of fractures remained due to fibrocystic hyperparathyroid osteodystrophy. Therefore an individualized treatment plan with anti-osteoporotic medication included 2 μg alfalcaldiol and 1,500 mg calcium. Postoperative follow-up was only for a further six months, and the further clinical outcome for this patient is unknown.

The male infant who appeared to be healthy at birth had hypocalcemia in the early neonatal period, and his condition deteriorated, characterized by rapid breathing and increased heart rate, the development of neurologic symptoms, including hypere excitability, limb tremor, muscle weakness, and increased tendon reflexes. Ultrasound of the brain showed no pathology. Laboratory test results showed a calcium level of 1.4 mmol/L (normal range, 1.90–2.60 mmol/L) and a phosphorus level of 3.84 mmol/L (normal range, 1.3–2.6 mmol/L). In the course of the treatment with calcium and magnesium supplements, the infant’s condition stabilized, and he was discharged from hospital. However, on the 16th day of life, the child was
hospitalized in the Children's Clinical Hospital No. 9 in Moscow and was suffering from convulsions, tachypnea, tachycardia, skin changes, perioral and periorbital cyanosis, and acrocyanosis. Laboratory tests showed total calcium of 1.29 mmol/L and an ionized calcium of 0.7 mmol/L. The seizures were diagnosed to be an effect of neonatal hypocalcemia following in utero parathyroid gland suppression due to maternal primary hyperparathyroidism. Treatment by intravenous administration of calcium and magnesium was initiated, and normocalcemia was achieved with a total calcium of 2.34 mmol/L and ionized calcium of 1.2 mmol/L, at which time, his seizures ceased. The infant’s condition improved and he was discharged from the hospital aged 33 days old.

Discussion

The prevalence of primary hyperparathyroidism during pregnancy is unknown, but it is an uncommon condition and often remains undiagnosed due to physiological changes during pregnancy that mask the symptoms, as in the case presented in this report. In this patient’s case, it is likely that the gestational primary hyperparathyroidism and its bone-related complications followed the first pregnancy, but primary hyperparathyroidism was not diagnosed at that time. The first tests for calcium levels were performed four years after the development of the initial symptoms. Hemodilution, hypoalbuminemia, increased fetal calcium requirements and increased urine calcium excretion in pregnant women can result in a total decrease in serum calcium by up to 20%, while ionized calcium levels usually remain unchanged [14]. The finding of an increased ionized calcium with a concomitant elevation in parathyroid hormone (PTH) levels, or that in the upper limit of normal, would be highly suspicious for the diagnosis of primary hyperparathyroidism during pregnancy.

Primary hyperparathyroidism during pregnancy is associated with significant risk of neonatal and maternal morbidity and mortality, but primary hyperparathyroidism and mild hypercalcemia during pregnancy can also be asymptomatic and clinically uneventful [8]. Symptoms of primary hyperparathyroidism are reported in up to 67% of affected women, which are mainly nonspecific and overlap with the common complaints during pregnancy, of fatigue, nausea, vomiting, constipation, and difficulty in concentrating. Severe complications of hypercalcemia include nephrolithiasis (24–36%), bone disease (13–19%), pancreatitis (7–13%), and hypercalcemic crisis [2]. Also, complications such as hyperemesis gravidarum and pre-eclampsia have been reported [15]. In the case of the patient in this report, a delayed diagnosis of primary hyperparathyroidism resulted in severe skeletal deformities and multiple fractures. Also, the patient developed renal complications, including nephrocalcinosis and microthiasis. Due to the high risk of perinatal and maternal pathology, and the development of pre-eclampsia the patient underwent a cesarean section at 37 weeks. Hultin et al. demonstrated a significant association between parathyroid adenoma and subsequent pre-eclampsia, and proposed that higher levels of serum PTH and calcium increase endothelial damage, insulin resistance, and cardiovascular disease and therefore increase the risk of pre-eclampsia risk [16]. Also, maternal vitamin D deficiency has been shown to be associated with the development of pre-eclampsia [16].

Routinely employed imaging modalities including contrast-enhanced computed tomography and (CT) and scintigraphy with technetium-99m-labeled methoxyisobutylisonitrile (99mTc-MIBI) should be avoided in pregnancy due to the radiation doses involved. Ultrasonography, which has 69% diagnostic sensitivity and 94% diagnostic specificity, is the preferred imaging modality in diagnosing of parathyroid adenoma in pregnancy, but the method is highly operator-dependent [17]. Ectopic parathyroid adenomas are not unusual, occurring in approximately 16% of initial surgery for primary hyperparathyroidism [18]. The most common location for ectopic parathyroid adenomas is the thymus, followed by retro-oesophageal, intrathyroidal, mediastinal and carotid sheath locations [18]. Non-invasive methods, such as CT and ultrasound, can locate potentially 50% of ectopic parathyroid adenomas, but if they fail, invasive, selective venous sampling of the internal jugular vein or angiography may be performed [19]. In this case, the diagnostic imaging was performed postpartum, which allowed for more sensitive imaging modalities to be used. No special studies beyond CT scan, ultrasound, and 99mTc-MIBI scintigraphy were used for detection of the adenoma. It should be noted that in many cases of ectopic parathyroid adenomas, patients had typically undergone one or several previous neck explorations before the tumor was located and removed [20].

Fetal complications in untreated mothers with primary hyperparathyroidism can affect 80% of newborn infants and can be fatal in between 20–30% of cases. Complications that affect the fetus include intrauterine growth restriction (IUGR), low birth weight, preterm delivery, and intrauterine fetal death. After delivery, the most dangerous complication is neonatal hypocalcemia [8,21]. Neonatal hypocalcemia occurs in more than 50% of cases and is usually transient, but in some cases, it can be permanent. Neonatal tetany occurs in 25% of cases. Neonatal hypocalcemia is secondary to elevated maternal calcium levels that suppress the fetal parathyroid glands. In this reported case, in the early neonatal period, postpartum hypocalcemia deteriorated sharply, characterized by the development of neurologic symptoms. Immediately after birth, a transfer to an intensive care unit (ICU) to determine calcium levels is necessary and to monitor the treatment response of hypocalcemia and tetany with calcium and vitamin D supplementation [22].
The treatment of primary hyperparathyroidism during pregnancy should be performed on an individualized basis. Management of this condition should be based on the patient's symptoms, the severity of hypercalcemia and gestational age of the fetus. In asymptomatic patients with mild hypercalcemia (<2.75 mmol/L), conservative treatment with oral hydration and low-calcium diet, with or without forced diuresis with a low dose of loop diuretic can produce good outcomes for both mother and child [23]. Effectiveness and safety of treatment options for primary hyperparathyroidism in pregnancy remain unknown, but when calcium levels rise above 2.75 mmol/L, parathyroidectomy is increasingly recommended [24]. The optimal time for surgery has generally been considered to be the second trimester, while management of clinically significant hypercalcemia in the third trimester remains controversial [17]. Operative complications or fetal loss related to surgery during pregnancy have not been previously reported. In this case report, primary hyperparathyroidism was diagnosed very late, at 37 weeks of gestation with the threat of premature birth. Therefore, cesarean section was first performed, and parathyroidectomy was completed on the 9th day after delivery. The severity of hypercalcemia in this case and the delayed diagnosis increased the risk of a poor outcome for both the mother and the child.

Conclusions

Primary hyperparathyroidism is more common in women, and it is typically diagnosed between the ages of 50–79 years. Primary hyperparathyroidism presenting at a young age, and during pregnancy, is uncommon. Primary hyperparathyroidism during pregnancy requires early diagnosis and treatment to reduce potential maternal and fetal complications. Screening for primary hyperparathyroidism should be performed in pregnant women with any symptoms associated with hypercalcemia. The treatment approach should be individualized to ensure the best outcome for each patient. Parathyroidectomy is the treatment of choice and seems to be safest beyond the second trimester. In some cases, as in this patient, parathyroidectomy may be successfully performed in the early postpartum period.

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Conflict of interest

None.

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