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Primary hyperparathyroidism in pregnancy — a diagnostic and therapeutic challenge

Pierwotna nadczynność przytarczyc w ciąży — wyzwanie diagnostyczne i terapeutyczne

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Abstract

Hypercalcaemia during pregnancy is uncommon, and mostly associated with primary hyperparathyroidism (pHPT). If unrecognised, it poses a significant risk for the mother and the foetus. Maternal symptoms include: hyperemesis, muscle weakness, pancreatitis, nephrolithiasis, bone disease, mental status changes, and hypercalcaemic crisis. Untreated disease complicates foetal development and foetal death is a significant risk. Our case illustrates the difficulty in detecting pHPT during pregnancy, serious complications connected with severe hypercalcaemia, and difficulties in preparing the patient for surgical treatment. Our review of the medical literature did not identify any previous case of a pregnant woman with hypercalcaemic crisis (total calcium 17 mg/dL, parathyroid hormone 2302 pg/mL), acute pancreatitis caused by pHPT, and with hyperthyroidism, who had undergone a successful surgical treatment. **(Endokrynol Pol 2015; 66 (3): 270–274)**

Key words: *primary hyperparathyroidism; hypercalcaemic crisis; pregnancy; acute pancreatitis*

Streszczenie

Hyperkalcemia w ciąży jest rzadko spotykanym zaburzeniem. Jej główną przyczyną jest pierwotna nadczynność przytarczyc (pHPT). Brak prawidłowo postawionego rozpoznania stanowi ryzyko zarówno dla matki, jaki płodu. Wśród objawów występujących u matki wymienia się wymioty, osłabienie siły mięśniowej, ostre zapalenie trzustki, kamicę nerkową, objawy kostne, zaburzenia psychiczne i przełom hiperkalcemiczny. Nieleczona hiperkalcemia może być przyczyną ograniczenia wzrostu, a także obumarcia płodu. Przedstawiony przypadek ukazuje trudności w rozpoznaniu pHPT w ciąży, poważne powikłania ciężkiej hiperkalcemii oraz trudności w przygotowaniu pacjentki do leczenia operacyjnego. W dotychczas opublikowanej literaturze według wiedzy autorów pracy nie przedstawiano przypadku ciężarnej z przełomem hiperkalcemicznym (całkowite stężenie wapnia 17 mg/dl, parathormon 2302 pg/ml), ostrym zapaleniem trzustki z towarzyszącą nadczynnością tarczycy, u której przeprowadzono skuteczne leczenie operacyjne. **(Endokrynol Pol 2015; 66 (3): 270–274)**

Słowa kluczowe: *pierwotna nadczynność przytarczyc; przełom hiperkalcemiczny; ciąża; ostre zapalenie trzustki*

Introduction

Primary hyperparathyroidism results from the excessive secretion of parathyroid hormone (PTH) and is caused by a single parathyroid adenoma. The disorder is common and usually asymptomatic. Primary hyperparathyroidism (pHPT) is uncommon in pregnancy and often goes undiagnosed due to gestational physiological changes. The majority of women with pHPT have a history of one or more miscarriages. Worsening of hypercalcaemia may cause a hypercalcaemic crisis during pregnancy or after delivery [1, 2]. Untreated disease complicates foetal development, and foetal death is a significant risk. The recommended treatment of pHPT is parathyroidectomy.

Case report

A 33-year-old woman was admitted to the gynaecological unit in the 14th week of her second pregnancy because of progressive weakness, severe abdominal pain, nausea, and vomiting. Her previous pregnancy ended in spontaneous miscarriage in the 10th week, in 2010. Medications used prior to hospitalisation included nonsteroid anti-inflammatory drugs (NSAID). The patient was seen for the first time in hospital in the 12th week of gestation with a diagnosis of acute kidney disease, probably due to NSAID and secondary hypertension.

On admission to the gynaecological unit the patient suffered from severe central abdominal pain radiating to her back. On physical examination dehydration,

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Table I. *Laboratory evaluation on admission*
Tabela I. *Ocena laboratoryjna przy przyjęciu*

	Patient's results	Normal ranges
White blood cells [10˜3/uL]	31.75	4.1–10.9
Creatinine [mg/dL]	1.9	0.7–1.2
eGFR (MDRD)	32	90–140
Urea [mg/dL]	61	10–50
Total serum calcium [mg/dL]	17.5	8.6–10.2
Albumin [g/L]	25.8	4–48
Phosphates [mg/dL]	5.3	2.7–4.5
Parathormone [pg/mL]	559.9	15.0–6 5.0
Lipase [U/L]	2219	13–60
Alfa-amylase [U/L]	2599	28–100
Urine amylase [U/L]	9114	≤ 460
TSH [ulU/mL]	0.01	0.27–4.2
fT4 [pmol/L]	51.3	11.8–24.6
TSH-receptor antibodies [U/L]	1.84	< 1.0
CRP [mg/dL]	3.56	0–0.5
D-dimer [ng/mL]	> 20	0–0.5
Glucose [mg/dL]	135	60–99
pH	7.24	7.35–7.45
HCO_3 [mmol/L]	14.3	22–26
BE [mmol/L]	–13.1	–3÷3
pO_2 [mm Hg]	69.8	80–100
Urine	Protein 58 mg/dL	Protein neg
	Glucose 300 mg/dL	Glucose neg
Urine centrifuged	> 100 WBC/HPF	Up to 5WBC/HPF

tachypnoea, tachycardia, and distended abdomen were found. Initial abnormal laboratory results obtained within 24 hours are presented in Table I. Alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, magnesium, sodium, potassium, chlorides, international normalised ratio (INR), lipids, and thyroid autoantibodies were within normal ranges. An ultrasound indicated that the patient had oedematous pancreatitis, ascites, trace amount of right pleural exudate, kidney — hyperechogenic cortex, and medulla layers. A neck ultrasound showed that the thyroid gland was not enlarged and was normoechogenic, but below the left lobe a hypoechogenic tumour of size 33 × 13 × 21 mm was found (Fig. 1). An obstetric ultrasound indicated a single pregnancy alive, with a biparietal diameter (BPD) of 30.43 mm and a femur length (FL) of 15.6 mm.

The treatment began with fasting, analgesia, intravenous fluids, antibiotics (clindamycin, metronidazole), dalteparin, hypotensive drugs (methyldopa, labetalol), furosemide, parenteral thiamazolum, and parenteral nutrition.

Acute pancreatitis (Apache II score 16), hypercalcaemic crisis in the course of pHPT, and thyrotoxicosis with impending storm (point scale for the diagnosis of thyroid storm — score 30) in the course of Graves' disease (GD), and acute kidney disease were diagnosed. The patient was transferred on the following day to an Intensive Care Unit (ICU).

On ICU admission the patient was conscious, anxious with malaise and tremor, face and palms flushing, abdominal pain, pruritus, borderline respiratory status with tachypnoea of 35 breaths per minute, blood pressure 165/100 mm Hg, tachycardia 135/min, renal dysfunction, hypercalcaemia (total calcium 17 mg/dL, ionized calcium 2,275 mmol/L), normothermia, with clinical severity status scored at 13 points according to the APACHE II score, and 41 points in SAPS 3 score. Treatment had been continued with continuous epidural analgesia (0.125% bupivacaine with fentanyl, pruritus disappeared after fentanyl dose reduction), thiamazole, hydration and furosemide under strict monitoring of haemodynamic parameters, treatment with propranolol, hydrocortisone, and total parenteral nutrition was introduced. Continuous veno-venous haemodialysis (CVVHD) with citrate anticoagulation due to concerns about extradural catheter was started for elimination of excess calcium and for renal dysfunction, with a target calcium level below total 9.5 mg/dL recommended for foetal safety. Improvement in clinical status and laboratory parameters was achieved with good control of pain and anxiety, blood pressure and heart rhythm, calcium level (symptoms of tetany in the form of paraesthesia at the upper normal levels of calcium were observed), thyroid hormones and renal parameters, pancreatic markers, and nutritional status. The patient became tranquil with significant improvement in mood, respiratory parameters and comfort, disappearance of pain, tremor and flushing, normotension, and heart rate within normal limits. Parenteral nutrition was changed to enteral nutrition within three days. In control abdominal ultrasound pancreatic oedema as well as abdominal and pleural effusions disappeared, and the foetus was alive. An increase in calcium level from the target level up to 13 mg/dL was observed between CVVHD sessions, regardless of adequate hydration and furosemide therapy. After appropriate preparation for surgery, total thyroidectomy and a single parathyroid adenoma excision were performed on the 9th ICU day. Intraoperatively, a decrease of PTH concentration from 2302 to 50.5 pg/mL was observed. Histological examination of the removed tissue confirmed the presence of a benign adenoma of the parathyroid gland. After surgery the patient

Figure 1. *The neck ultrasound — below the left lobe a hypoechogenic tumour of size 33 × 13 × 21 mm*
Rycina 1. *USG szyi — pod lewym płatem guz hipoechogeniczny o wymiarach 33 × 13 × 21 mm*

was extubated, the last session of CVVHD introduced and thiamazole discontinued, L-thyroxin started, and hydrocortisone gradually discontinued. The patient was transferred to the Department of Endocrinology on the 11th ICU day in good clinical condition. During the postoperative period hypocalcaemia requiring supplementation was observed (hungry bone syndrome). In addition, vitamin D deficiency was diagnosed and cholecalciferol was introduced. Gestational diabetes was recognised in the 17th week of pregnancy. Because of insufficient glucose control during diet regimen, insulin treatment was introduced. Antihypertensive therapy was not necessary.

The patient was admitted to the gynaecological unit in the 27th week of gestation because of suspicion of intrauterine growth retardation (IUGR). On admission, her blood pressure was above 140/90 mm Hg, laboratory results indicated calcium levels at 8.4 mg/dL, phosphates at 2.4 mg/dL, PTH at 91.52 pg/mL, proteinuria at 228 mg/day, haemoglobin at 10.6 g/dL and HbA_{1c} at 5.1%. Treatment with calcium carbonate, cholecalciferol, L-thyroxin, ferrous chloride, dalteparin, and insulin were continued. Antihypertensive therapy was reintroduced. An obstetric ultrasound showed FL < 3rd percentile, the abdominal circumference (AC) at 3rd percentile, BPD at the 80th percentile, and the head circumference (HC) at the 23rd percentile. The next hospitalisation started in the 34th week of gestation. A gestational ultrasound found that AC, FL, BPD, and HC were < 3rd percentile. Laboratory parameters were stable. In the 36th week, because of the absent end-diastolic flow in the umbilical artery and low cerebro-placental ratio of 0.39, gestation was ended with caesarean section. A live-born infant, a male weighing 1600 g (< 10th percentile) was born with Apgar score of 8. Signs of respiratory insufficiency were noted on physical examination requiring continuous positive airway pressure for three hours. The total serum calcium concentration was within normal limits. Hypoglycaemia, needing intra-venous glucose infusion, was observed during the first hour after delivery. From the 2nd neonatal day the baby's general condition was stable. The newborn was breastfed. During ultrasound of heart and central nervous system no abnormalities were observed.

On the 17th day of the puerperium the patient was discharged from the hospital with the baby (whose body weight had increased to 2180 g). Treatment with calcium carbonate, cholecalciferol, L-thyroxin, and dalteparin were continued. Insulin treatment was discontinued after the delivery.

Discussion

Calcium homeostasis is a very stable mechanism. PTH is one of the principal factors in the prevention of hypocalcaemia. The haemodilution observed during pregnancy results in the fall of serum albumin. As a result, the total serum calcium falls while the ionised

calcium remains constant during pregnancy. The physiological changes associated with pregnancy, such as the active transport of blood from mother to foetus and increased urine calcium excretion in pregnant women, also affect the total calcium serum concentration. The normal ranges of calcium concentration for pregnant women are lower compared with the total population. Undiagnosed cases of pHPT may be connected with these pregnancy related changes. Complications associated with pHPT in pregnancy have been reported to occur in up to 67% of mothers and in 80% of foetuses. Maternal complications include nephrolithiasis, bone disease, pancreatitis, mental status changes, and hypercalcaemic crisis [1]. The mother is especially at risk of hypercalcaemic crisis after delivery, when no treatment is provided. There are also reported complications specific to pregnancy — hyperemesis gravidarum and preeclampsia [2, 5, 6]. Hypercalcaemic crisis is a very rare condition occurring during pregnancy. Only a few cases have been reported [7]. Other clinical findings, such as maternal hypertension, were also noted; however, this association remains inconclusive. Acute pancreatitis in pregnancy is a rare condition and pHPT is a potential aetiological factor.

Maternal and foetal complications, however, cannot be predicted based on duration or severity of hypercalcaemia. In pHPT during pregnancy active transport of calcium ions from mother to foetus leads to suppression of the foetal parathyroid glands. After delivery the mother may suffer from worsening hypercalcaemia or even hypercalcaemic crisis since the active transport of calcium from mother to foetus is disrupted, but this life-threatening condition may occur also during pregnancy. On the other hand, a newborn may develop hypocalcaemic tetany [2, 3].

In the patient described in this case, hypercalcaemic crisis caused by pHPT coexisted with life-threatening thyrotoxicosis, acute pancreatitis, and hypertension. Life-threatening thyrotoxicosis or thyroid storm is a rare disorder characterised by a high mortality rate if not immediately recognised and treated aggressively. In our patient without previous history of GD thyrotoxicosis, the impending thyroid storm was probably connected with severe acute pancreatitis and hypercalcaemic crisis. Gestational diabetes, which was later recognised, also influenced foetal growth.

The evaluation of appropriate foetal growth and the diagnosis of its disorders are essential elements in the care of pregnant women. Reported foetal complications include intrauterine growth retardation, low birth weight, premature birth, intrauterine foetal demise, postpartum neonatal tetany, and permanent hypoparathyroidism [2, 7]. A pregnancy complicated by intrauterine growth restriction is a pregnancy of high risk. We observed that hypertension and gestational diabetes also influenced the neonatal growth in our patient.

The correct diagnosis of primary hyperparathyroidism in pregnancy is essential. Primary hyperparathyroidism is diagnosed when PTH is elevated in the context of hypercalcaemia. Sometimes serum calcium levels fluctuate into the upper normal range and their repeated measurements are necessary. In patients with subtle pHPT, intermittent hypercalcaemia may occur. In patients with pHPT, low or low-normal serum phosphorus is noticed. Elevated or even upper-normal levels of the intact PTH level in the case of hypercalcaemia confirm hyperparathyroidism or one of its variants (familial benign hypocalciuric hypercalcaemia). The physiological changes observed in pregnancy should also be taken into consideration.

The use of preoperative localisation techniques in pregnant women is limited. Ultrasound plays the basic diagnostic role. Technetium-99m sestamibi scanning was also reported in cases with ectopic localisations of parathyroid adenoma [8]. Intra-operative PTH hormone monitoring is also a helpful diagnostic method.

Treatment of hypercalcaemia in pregnant woman is not different from that in non-pregnant women. Dehydration should be corrected by intravenous fluid administration. Loop diuretics are administrated to promote calcium diuresis. In the case of hypercalcaemic crisis, the patient requires intensive treatment. The application of bisphosphate is contraindicated in pregnant women (category C); however, it can be used after delivery. Calcitonin, because of its limited effect due to tachyphylaxis and category C, was not utilised [3, 6]. There have been a few cases where cinacalcet was administrated during pregnancy or postpartum. If diuresis does not give satisfactory results by lowering the serum calcium, dialysis should be performed [3]. Diagnostic testing should be conducted in parallel with calcium lowering treatment. The only definitive treatment of pHPT is parathyroidectomy [8]. There is general agreement that parathyroidectomy should be performed in pregnant women during the second trimester. In the case of symptomatic hypercalcaemia, surgical treatment can also be performed by an experienced surgeon even in the third trimester of pregnancy [1, 7].

Conclusions

In conclusion, clinical evidence of symptoms, signs, diagnosis, and treatment of pHPT in pregnancy is limited. The severity of the disease is classified by calcium levels. Additional conditions, as well as gestational age, also influence the choice of treatment. The above-described pregnant patient with hypercalcaemic crisis and acute pancreatitis caused by pHPT with coexisting

hyperthyreosis underwent successful surgical treatment in the 15th week of pregnancy. In the 36th week the gestation was ended by caesarean section. The live-born infant did not present abnormal calcium levels.

The key factor for further reduction of maternal and foetal mortality is early awareness and recognition of the potential presence of a pHPT in a pregnant patient with history of miscarriage and clinical signs of hypercalcaemia.

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