



Primary Hyperparathyroidism in Pregnancy: Insights From a Case of a 28-Year-Old Woman With Miscarriages and Hyperemesis Gravidarum

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Dear Editor,

Serum calcium level usually decreases during pregnancy due to hemodilution; thus, hypercalcemia in pregnancy should be followed by parathyroid hormone (PTH) measurement to exclude parathyroid dysfunction. We report a case of severe hyperemesis gravidarum combined with hypercalcemia that led to two consecutive pregnancy losses. This report was approved by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Beijing, China (2017-KY-011-02) and was conducted in accordance with the 1964 Helsinki Declaration and its amendments. The study protocol was approved by the Institutional Committee on human research. The patient provided written informed consent to publish her case. In July 2019, a 28-year-old pregnant woman at 13 gestational weeks (GWs) presented to the Internal Medicine Department of Beijing Obstetrics and Gynecology Hospital, Beijing, China, with a chief complaint of intermittent nausea and vomiting. During this visit, the patient tested positive

for urine ketone bodies (+4), hypokalemia, and hypercalcemia (Table 1). Neither kidney stone nor nephrocalcinosis was found in abdominal ultrasound examinations. After necessary nutritional supplementation, she tested negative for urinary ketone bodies. With a diagnosis of hyperemesis gravidarum and hypercalcemia of unknown origin, the patient was discharged and referred to the Endocrinology Department for further evaluation. Notably, the patient was diagnosed as having hyperemesis gravidarum accompanied by hypercalcemia, and she had a miscarriage at 10 GWs three years ago.

The patient consulted an endocrinologist at GW 14, and her laboratory workup results showed elevated intact PTH (iPTH) and serum calcium levels, and low serum phosphorus level (Table 1). Ultrasonography of the parathyroid gland revealed a lesion of approximately 0.6×0.4 cm at the posterior pole of the left lobe of the parathyroid. The lesion was hypoechoic and inhomogeneous, with a clear border and visible blood flow signals

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detected by color Doppler flow imaging (HITACHI Ascendus, Tokyo, Japan). These results were consistent with a diagnosis of parathyroid hyperplasia or primary hyperparathyroidism (PHPT) in light of the hypercalcemia and increased serum iPTH level. At GW 17, ultrasound-guided microwave ablation (MWA) of the parathyroid gland was performed under local anesthesia with lidocaine. Although the patient's iPTH, serum calcium, and phosphorus levels returned to normal shortly after the intervention (Table 1), she was admitted again at GW 19 for severe malnutrition and experienced miscarriage followed by induced abortion.

PHPT causes excessive PTH secretion, which can lead to osteoporosis, kidney stones, fragile fracture, high calcium crisis, and serious maternal and fetal adverse outcomes during pregnancy [1]. A previous study indicated that 68% of pregnant women with PHPT experienced maternal complications such as preeclampsia, polyhydramnios, and spontaneous abortion, and 80% suffered fetal/neonatal complications such as fetal growth restriction, intrauterine fetal death, neonatal tetany, and neonatal death [2]. Among cases of miscarriage associated with PHPT, the severity of the complications was positively correlated with the elevated serum calcium levels [3]. More strikingly, 72% of pregnant women with PHPT have had at least one spontaneous miscarriage [4]. However, the common but non-specific clinical

presentations of PHPT, such as nausea, vomiting, and fatigue, are similar to those of pregnancy, and therefore PHPT diagnosis is often missed or inappropriately treated as plain hyperemesis gravidarum. An additional challenge in the diagnosis of PHPT in pregnancy is that serum calcium is physiologically hemodiluted during pregnancy, and thus its pathological increase is much less noticeable.

Surgery is recommended for patients with PHPT in pregnancy, if the serum calcium level is ≥ 2.85 mmol/L; if it is < 2.85 mmol/L, conservative treatment such as a low calcium diet, hydration, diuresis, and/or calcitonin administration should be considered [5]. Some experts have suggested that surgery should be performed when the serum calcium level is > 3 mmol/L, and that the intervention strategy should be determined by the gestational stage, hypercalcemia severity and symptoms, and patient preference [6]. In the present case, the patient received MWA instead of conventional surgery to avoid potential adverse effects due to general anesthesia, surgery wound, and bleeding. MWA has been successfully adopted as a minimally invasive therapeutic alternative to surgery for some patients, including pregnant women, who are intolerant to or unwilling to undergo parathyroidectomy under general anesthesia [7].

A literature review revealed three similar reports on hyperemesis gravidarum combined with PHPT in pregnancy (Table 2) [8 - 10]. All three cases underwent parathyroidectomy but had diverse pregnancy outcomes. In the present case (case 4 in Table 2), miscarriage occurred three weeks after MWA, which was likely due to the long-term malnutrition and hyperparathyroidism condition.

In summary, serum calcium and PTH levels should be monitored in pregnant women who present with severe and constant hyperemesis gravidarum to exclude the possibility of PHPT, which poses a significant risk of maternal/fetal complications, including miscarriage.

Table 1. Serum calcium, phosphorus, and iPTH levels in the clinical course of the patient

Major clinical event	Pre-MWA		Post-MWA		Miscarriage
Gestational weeks	13	14	17	19	21
Serum calcium (mmol/L)*	2.87	2.72	1.78	1.82	1.81
Serum phosphorus (mmol/L)*	0.58	0.62	0.56	0.88	1.14
iPTH (pg/mL)*	165.3		27.3		

*Reference intervals: serum calcium, 2.10–2.55 mmol/L; serum phosphorus, 0.74–1.52 mmol/L; iPTH, 12–88 pg/mL.

Abbreviations: iPTH, intact parathyroid hormone; MWA, microwave ablation.

Table 2. Clinical cases of PHPT with hyperemesis gravidarum in pregnancy

Characteristics	Case 1 [8]	Case 2 [9]	Case 3 [10]	Case 4 [Present case]
Age (yr)	27	22	23	28
Gestation history	G1P0	G2P1	G1P0	G2P0
Average serum calcium level (mmol/L)	2.92	4.38	3.19	2.96
Gestational age of diagnosis (week)	17	11	15	14
Intervention	Parathyroidectomy	Parathyroidectomy	Parathyroidectomy	MWA
Pregnancy outcome	Intrauterine death	Preeclampsia	Uncomplicated	Intrauterine death
Delivery outcome	Miscarriage	Cesarean section	Vaginal delivery	Miscarriage

Abbreviations: PHPT, primary hyperparathyroidism; G, gravidity; P, parity; MWA, microwave ablation.

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AUTHOR CONTRIBUTIONS

Study conception and design: Zhang L, Gao H, and Cao Z. Data acquisition and analysis: Zhang L and Hu Y. Analysis and interpretation of the data: Zhang L, Zhai Y, and Cao Z. Writing the manuscript: Zhang L and Cao Z. Reviewing and editing the manuscript: Zhang L, Luo YR, Zhai Y, and Cao Z. Final approval of the manuscript: Zhang L, Hu Y, Luo YR, Zhai Y, Gao H, and Cao Z.

CONFLICTS OF INTEREST

The authors state that there are no conflicts of interest with regard to publication of this article. The funding organizations played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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