

# Primary Hyperparathyroidism Diagnosed during the Work-up of Hydrops Fetalis: A Case Report

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## **Abstract**

*While rare in pregnancy, unrecognized primary hyperparathyroidism (PHPT) may pose significant risks to both maternal and fetal health. While the majority of non-pregnant individuals are diagnosed incidentally with PHPT after routine laboratory screening, serum calcium levels are not routinely ordered in pregnancy and many expectant mothers may go undiagnosed. We present a case of non-immune hydrops and fetal demise diagnosed at 25 weeks gestation in a 24 year-old primigravida. Her workup for hydrops fetalis was negative other than an elevated calcium level which was incidentally noted on routine lab-work, low phosphorus, and elevated parathyroid hormone. Following delivery of a non-viable fetus, ultrasound and Sestamibi scans confirmed the presence of a parathyroid adenoma, which was later removed surgically. The literature suggests that fetal and maternal complication rates from PHPT are high. Fetal complications include preterm birth, stillbirth, and growth restriction. Fetal demise in PHPT occurs at 3.5 times the known rate of pregnancy loss in the general population. Symptomatic PHPT can be safely managed during pregnancy with parathyroidectomy ideally occurring in the second trimester.*

## **Keywords**

*Hyperparathyroidism in pregnancy, primary hyperparathyroidism, hypercalcemia, stillbirth, intrauterine fetal demise*

## I. Introduction

The incidence of primary hyperparathyroidism (PHPT) in pregnancy is rare, comprising less than 1% of all patients with hyperparathyroidism [1,2]. The overall incidence of PHPT in the general population is estimated to be 0.1-0.4%, [3,4] and 8% of cases occur in women of child-bearing age [1]. However, the incidence of this disease during pregnancy is likely underestimated, as many cases go undiagnosed [5]. Among women of child-bearing age, the incidence of PHPT has been estimated at 8 cases per 100,000 population per year [6].

The most common cause of PHPT in pregnancy is a single parathyroid adenoma, present in about 85% of cases. Primary hyperplasia of the four glands accounts for about 10% of the cases reported. Two percent are due to multiple adenomas, and about 1% is due to parathyroid carcinoma [7]. In rare cases, PHPT can also be caused by multiple endocrine neoplasia or other genetic syndromes [4].

## II. Patients and Methods

A 24 year-old primigravida at 25.0 weeks gestation who presented with a history of poorly controlled chronic hypertension underwent a detailed anatomy scan for findings of elevated maternal serum alpha fetoprotein levels. On ultrasound, hydrops fetalis was noted and the patient was

transferred to Virginia Commonwealth University Medical Center in March 2010 for evaluation of non-immune hydrops.

Upon presentation, an intrauterine fetal demise was discovered. The patient was subsequently induced and underwent an uncomplicated vaginal delivery. A serologic workup for non-immune hydrops was performed, eventually yielding negative results (Table 1). Included in the workup of the mother was a comprehensive metabolic panel. An elevated serum calcium of 13.5 mg/dL (9.0-10.5) was incidentally noted. Further workup revealed low phosphorus of 1.8 mg/dL (3.0-4.5) and an elevated parathyroid hormone of 404 pg/ml (12-65). At this point, the level of suspicion was high for a working diagnosis of hyperparathyroidism. An ultrasound of the neck was performed and showed a 3.5 x 1.5 x 2.0 centimeter nodule with mixed heterogeneity arising from the right lobe of the thyroid. A detailed Sestamibi scan then showed a mass with increased tracer uptake posterior and inferior to the thyroid consistent with a parathyroid adenoma. Departments of Endocrinology and Surgery were consulted prior to the patient's discharge home from the hospital with appropriate outpatient follow up in place.

Two months following discharge, the patient underwent an uncomplicated right inferior parathyroidectomy. Her calcium levels returned to normal immediately after excision.

Final histopathology reported a benign parathyroid adenoma.

### III. Discussion

In a review of 70 pregnant women with PHPT, gastrointestinal symptoms such as nausea, vomiting and anorexia were present in 36% of patients, whereas 34% presented with weakness and fatigue. In 26%, neurobehavioral symptoms, including headache, lethargy, agitation, emotional lability, confusion, and inappropriate behavior were reported [8]. However, among non-pregnant women, up to 70% of patients are asymptomatic and the diagnosis is made after routine laboratory screening [9]. In contrast, as calcium determinations are not routinely performed in pregnancy, symptoms are present in almost 70% of patients diagnosed with PHPT during pregnancy [10]. Additionally, signs and symptoms of PHPT may be less evident in pregnancy since they are attenuated by physiological changes associated with pregnancy. Low serum albumin, increased placental calcium transport, and an increased glomerular filtration rate result in lower calcium levels in pregnancy. In addition, resorption of bone due to the action of parathyroid hormone (PTH) is inhibited by increased estrogens in pregnancy [11]. The combination of these factors makes PHPT difficult to detect in early pregnancy. The rate of maternal complications during pregnancy associated with PHPT has been reported to be as high as 67%. [2,5] The most

common complications during pregnancy reported in one study were nephrolithiasis (13%), bone disease (19%), acute pancreatitis (13%), and hypertension (10%), and 24% of women remained asymptomatic. In another study, pre-eclampsia was diagnosed in 25% of patients [12]. Occasionally, life-threatening complications such as acute pancreatitis and hypercalcemic crisis can occur. Pancreatitis is more common in pregnant patients with PHPT (13%) than in non-pregnant patients with the disease (1.5%) or in pregnancy alone (<1%) [13]. Hypercalcemic crisis occurs as calcium levels approach 14 mg/dL and presents with nausea, vomiting, dehydration, weakness, and mental status changes. It can rapidly progress to uremia, coma, and death. Hypercalcemic crisis may occur during pregnancy or postpartum, as worsening of hypercalcemia may occur after separation of the placenta since the placenta transports excess calcium to the fetus while still attached [14,15].

Previous studies have reported a fetal and neonatal complication rate of 45-80% associated with maternal PHPT [2,16]. Intrauterine and neonatal complications of PHPT may include preterm premature rupture of membranes, preterm birth, spontaneous abortion, stillbirth, intrauterine growth restriction, fetal tetany, seizures, hypotonia, jitteriness, low birth weight, and respiratory distress syndrome requiring intubation [12].

The overall risk of fetal and neonatal mortality is approximately 30% [3]. In one study by Norman et al., parathyroidectomy was successfully performed on 15 patients (19.5% of patients) during the second trimester and all of these women went on to have uncomplicated deliveries of healthy infants from 36 to 40 weeks gestation [1]. Out of the remaining 62 pregnancies, almost half (48%) were lost, a rate that is 3.5-fold higher than the known rate of pregnancy loss in the general population. Pregnancy loss typically occurred in the late first and early second trimester, with second trimester losses (30%) being six-fold higher than expected. Fetal loss was seen at all levels of elevated maternal calcium, but most were seen above 11.4 mg/dL, and the rate of fetal loss increased with increasing maternal serum calcium levels. For the highest levels of serum calcium (in the range of 12.2 – 13.0 mg/dL), the fetal loss rate was 80% [1]. Hirsch et al. found that in a cohort of only mildly hypercalcemic pregnant women, rates of spontaneous abortion and complications were not increased, further supporting that outcomes are linked with the degree of calcium elevation [5]. In a study of mothers treated surgically after 27 weeks gestation, 17.6% to 23.5% of clinically significant fetal complications occurred due to delayed diagnosis or postponed surgery [12].

Up to 22%-50% of cases with maternal hypercalcemia may lead to neonatal hypocalcemia and tetany [16-18]. Neonatal hypocalcemia occurs in the setting of persistent maternal hypercalcemia because the development of the parathyroid glands is stunted, and these infants are therefore unable

to secrete adequate amounts of PTH to regulate serum calcium [19,20].

The diagnosis of PHPT is based on persistent hypercalcemia in the presence of increased serum PTH levels [3]. A persistent serum ionized calcium level value higher than 9.5 mg/dL should make the examiner suspicious of hypercalcemia [17]. It is important to evaluate the ionized calcium level, since normal physiological changes during pregnancy cause an increase in extracellular volume and a decrease in albumin, resulting in a falsely low calcium level although the ionized calcium is normal [21]. Serum phosphorous is decreased in about 50% of pregnant women with PHPT. A determination of 24-hour urinary calcium excretion is helpful in the diagnosis, because most women with PHPT have an increase in urinary calcium excretion that is higher than the usual hypercalciuria of normal pregnancy [17]. Urinary calcium excretion is low or low-normal in the syndrome of familial hypocalciuric hypercalcemia, another cause of hypercalcemia that should be included in the differential diagnosis [3]. Computed tomography and Sestamibi scans are not recommended in pregnancy due to the risk of exposing the fetus to ionizing radiation [3,7]. In pregnancy, parathyroid localization with ultrasound of the neck is considered first-line [3]. Ultrasound has a sensitivity of 69% and a specificity of 94% for detecting parathyroid disease [22]. In one study, 64% of cases parathyroid adenomas were successfully detected by ultrasound [1]. In the event that suspected PHPT is not detected by ultrasound,

magnetic resonance imaging is considered safe during pregnancy [14].

Most authors agree that symptomatic PHPT should be managed surgically in pregnancy, with parathyroidectomy ideally occurring in the second trimester [1, 8, and 23]. Surgery is the treatment of choice when serum calcium is greater than 11 mg/dL [3]. Studies have shown that women who remain hypercalcemic throughout pregnancy have a higher rate of complications than women who undergo parathyroidectomy during pregnancy [24]. In the face of improvements in safety of general anesthesia during pregnancy and because of the significant risk to both mother and infant associated with this disease, parathyroidectomy has been increasingly recommended [14]. Parathyroidectomy can also be performed without complication for symptomatic women who present in the third trimester [12, 23]. On the other hand, symptom-free patients may be managed medically and may undergo surgery in the postpartum period, especially if only mildly hypercalcemic [15]. Norman et al. determined that the majority of pregnancies are lost due to PHPT between 10 and 15 weeks and advocated for surgical management in the early second trimester, particularly if the mother's serum calcium is  $\geq 11.4$  mg/dL and for those with a previous history of pregnancy loss [1]. Postoperative hypocalcemia is a common side effect of parathyroidectomy, but is treatable [12].

Lifestyle interventions for treatment of mild hypercalcemia include a low or normocalcemic diet guided by nutritionist meal planning. Medical interventions that are

considered safe in pregnancy include oral phosphates, furosemide (a calcium wasting diuretic), and calcitonin [14]. Bisphosphonates are not typically recommended during pregnancy as they cross the placenta [25].

In conclusion, we present the case of a patient diagnosed with PHPT after an intrauterine fetal demise. This case report supports the utility of a screening serum calcium level in the work-up of intrauterine fetal demise. An elevated serum calcium would be suggestive of PHPT, which has negative effects on maternal and fetal health and is safely treatable in pregnancy.

#### **AUTHOR DISCLOSURE STATEMENT**

No competing financial interests exist.

Table 1. Results of laboratory work up for this case of hydrops fetalis

Test	Result
Blood Type	A Negative
Antibody Screen	Negative
Kleihauer-Betke	Negative
Toxoplasma IgG/IgM	Negative/Negative
Rubella IgM	Negative
CMV IgG/IgM	Positive/Negative
HSV 1 IgG/IgM	Positive/Negative
HSV 2 IgG/IgM	Positive/Negative
Parvovirus IgG/IgM	Positive/Negative
Thyroid Stimulating Hormone	Normal



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