Primary Hyperparathyroidism in Pregnancy: A Multicenter Case Series of 4 Patients from Northern India

Ajay Aggarwal¹ · Roopak Wadhwa¹ · Vivek Aggarwal² · Arun Pande³ · Swadesh Kumar Singh⁴ · Ankur Gahlot⁵ · Deependra Narayan Singh⁶ · Abhinav Sharma⁷

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About the Author

Dr. Ajay Aggarwal is a Senior Consultant and In-Charge, Department of Endocrinology, Fortis hospital, Shalimar Bagh, New Delhi. He did M.D. (Medicine) from Punjab University, Chandigarh, in 1998 and D.M. (Endocrinology) from Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow (U.P.) in 2004. His major areas of interest include diabetes, parathyroid disorders and thyrotoxicosis. He has published many papers in various journals and delivered talks in many national and international conferences. He has won best paper presentation awards twice at Endocrine Society of India (ESI) annual conference (ESICON) in 2002 and 2003. He is also running successfully a private endocrine clinic in North Delhi. He is also working as principal investigators (PI) in various multinational clinical trials. He is member of many national and international medical societies.

Introduction

Primary hyperparathyroidism (PHPT) is third most common endocrine disorder. Middle-aged women suffer three times more than men. The annual incidence of PHPT in pregnancy is around 8 cases per 100,000 of population [1].

Dr. Ajay Aggarwal, MD, DM, is a Senior Consultant, Department of Endocrinology, Fortis Hospital, New Delhi. Dr. Roopak Wadhwa, DNB, is a Consultant, Department of Endocrinology, Fortis Hospital, Shalimar Bagh, New Delhi. Dr. Vivek Aggarwal, MS, MCh, is a Consultant, Department of Endocrine Surgery, Fortis Hospital, Shalimar Bagh, New Delhi. Dr. Arun Pande, MD, DM, is a Consultant, Department of Endocrinology, Sahara Hospital, Lucknow, U.P. Dr. Swadesh Kumar Singh, MD, is a Consultant, Department of Medicine, Sahara Hospital, Lucknow, U.P. Dr. Ankur Gahlot, MD, DM, is a Consultant, Department of Endocrinology, Fortis Escorts Hospital, Jaipur, Rajasthan. Dr. Deependra Narayan Singh, MS, MCh, is a Consultant, Department of Surgery, Fortis Escorts Hospital, Jaipur, Rajasthan. Dr. Abhinav Sharma, MD, DM, is a Senior Consultant, Department of Gastroenterology, Fortis Escorts Hospital, Jaipur, Rajasthan.

✉ Ajay Aggarwal
endocrinologist39@yahoo.co.in

¹ Department of Endocrinology, Fortis Hospital, Shalimar Bagh, New Delhi, India

² Department of Endocrine Surgery, Fortis Hospital, Shalimar Bagh, New Delhi, India

³ Department of Endocrinology, Sahara Hospital, Lucknow, U.P., India

⁴ Department of Medicine, Sahara Hospital, Lucknow, U.P., India

⁵ Department of Endocrinology, Fortis Escorts Hospital, Jaipur, Rajasthan, India

⁶ Department of Surgery, Fortis Escorts Hospital, Jaipur, Rajasthan, India

⁷ Department of Gastroenterology, Fortis Escorts Hospital, Jaipur, Rajasthan, India

The physiological changes during normal pregnancy, like slight drop in serum calcium due to gestational hypoalbuminemia, increased glomerular filtration rate, transplacental transfer and low-normal intact parathyroid hormone (PTH), may obscure the diagnosis. However, ionized calcium levels are similar to that of non-pregnant state. So, PHPT in pregnancy may be more frequent than previously reported. The three major pathological conditions associated with PHPT include parathyroid adenoma, hyperplasia and carcinoma. Approximately, 85% cases of PHPT in pregnancy are due to single adenoma. The symptoms are usually non-specific as they overlap with those of pregnancy.

The maternal and fetal complications related to PHPT in pregnancy have been reported in 67 and 80% cases, respectively [2]. The maternal complications include pancreatitis, nephrolithiasis, preeclampsia, hypertension, peptic ulcer and muscle weakness. The fetal risks are intrauterine growth retardation, prematurity, permanent hypoparathyroidism and fetal loss.

Early diagnosis and proper treatment may reduce these complications significantly. The conservative approach is preferred in mild forms and surgery in symptomatic cases. Medical management, hydration with or without forced calciuresis, calcitonin and calcimimetics, has been reported to be effective [3]. Bisphosphonates have been used to lower calcium in cases of life-threatening hypercalcemia. Parathyroid surgery is recommended during second trimester [4]. Here, we present a series of 4 cases of PHPT in pregnancy and review the literature.

Methods

This is a multicenter case series comprising of 4 patients who were treated for PHPT in pregnancy at referral hospitals in New Delhi, Lucknow (Uttar Pradesh) and Jaipur (Rajasthan) across northern India. The data collected included presenting complaints, pre- and postoperative biochemical investigations, imaging, treatment opted and patient outcome.

Results

The demographic characteristics, symptoms, pre- and postoperative biochemistry, imaging findings, operative procedure and patient outcome are detailed in Tables 1 and 2. No patient had family history of multiple endocrine neoplasia (MEN). All patients had normal renal functions except patient 3. Radionuclide scan was not done due to the risk of teratogenicity. The postoperative period was

uneventful, and patients were discharged on oral calcium and vitamin D.

Patient 1 had repeated vomiting, increased thirst and polyuria for last 2 months. Her complaints were progressive in nature.

Patient 2 presented during 9th week of pregnancy. She improved on conservative management, and parathyroid surgery was deferred till second trimester for safety.

Patient 3 had conceived through vitro fertilization (IVF) and was bedridden for 1 week due to vaginal bleed. On examination, she was pale, dehydrated with tachycardia (104/min) and low blood pressure (80/60 mmHg). Along with severe hypercalcemia, her thyroid function test suggested thyrotoxicosis. There was no past history of thyroid illness. She also had sepsis and multi-organ dysfunction (deranged liver and kidney functions). Patient was managed in intensive care unit as sepsis with PHPT in pregnancy and thyrotoxicosis. USG neck for thyroid and parathyroid glands could not be done as she succumbed to death unfortunately.

Patient 4 presented during 32nd week of gestation with a 3-day history of severe nausea and vomiting. Laboratory evaluation confirmed the diagnosis of PHPT in pregnancy with acute pancreatitis. Figure 1 depicts the high-resolution USG neck picture showing parathyroid adenoma ($2.8 \times 2.6 \times 1.5$ cm) with increased vascularity at lower pole of left lobe of thyroid gland. Gross and histopathologic features of adenoma in this case are shown in Fig. 2. Histopathology revealed chief-cell-type of parathyroid adenoma. Her serum amylase and lipase values were very high, 348 and 1704 U/L, respectively. MRI abdomen was suggestive of acute pancreatitis. After parathyroid surgery, acute pancreatitis resolved gradually with normalization of pancreatic enzymes on conservative management.

Discussion

PHPT, most common cause of hypercalcemia in the outpatient setting, has a prevalence of 0.15% in the general population [1]. PHPT in pregnancy is uncommon entity with negative impact on maternal and fetal health. It remains often undiagnosed until the child birth as screening for PHPT is not done usually during pregnancy. A relatively low serum calcium level during pregnancy is caused by the physiological changes which affect calcium homeostasis. So, an increase in corrected or ionized calcium with normal or elevated PTH in pregnancy points to PHPT. Ionized calcium may be a more accurate reflection of calcium levels. Other possible causes of hypercalcemia should be ruled out. Familial hypocalciuric hypercalcemia (FHH) can be ruled out by quantifying low/normal 24-h urinary calcium. In a young patient with PHPT, hereditary

Table 1 Demographics, symptoms, treatment and patient outcome

Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	29	24	38	29
Trimester at diagnosis	Second	First	Second	Third
Symptoms	Body aches, walking difficulties	Pain abdomen, renal stones	Vomiting, weakness	Severe pain abdomen
Medical management	Hydration	Hydration	Hydration, calcitonin, intravenous pamidronate	Hydration, calcitonin
Trimester at surgery	Second	Second	–	Third
Operation done	MIP	MIP	–	MIP
Patient outcome	Cured	Cured	Died	Cured

Table 2 Pre- and postoperative biochemical investigations and preoperative imaging report

Investigations	Patient 1	Patient 2	Patient 3	Patient 4
Preoperative corrected calcium (mg/dl)	16.1	12.8	21.6	17.8
Preoperative PTH (pg/ml)	1187.6	760	1296	905
Preoperative 24-h urinary calcium (mg/24 h)	743.8	687.5	–	–
Postoperative corrected calcium (mg/dl)	9.8	8	–	7.5
Postoperative PTH (pg/ml)	< 2.5	16.4	–	12.5
Imaging (USG neck)	Right inferior parathyroid adenoma (2.3 × 1.5 × 1.2 cms)	Right superior parathyroid adenoma (2.2 × 2.1 × 1 cms)	–	Left inferior parathyroid adenoma (2.8 × 2.6 × 1.5 cms)
Histopathology	Confirmed	Confirmed	–	Confirmed

syndromes like multiple endocrine neoplasia (MEN 1, MEN 2), jaw tumor syndrome or familial parathyroid hyperplasia syndrome should be looked for.

Although majority of patients with PHPT in pregnancy are asymptomatic and are only diagnosed incidentally, all our 4 patients had symptomatic course like kidney stones, nausea, vomiting, bone pains, pain in abdomen, lethargy and fatigability due to severe hypercalcemia. They may have been diagnosed because of symptomatic course.

Ultrasound neck is the imaging technique of choice during pregnancy for localization, with sensitivity and specificity of 69 and 94%, respectively [5]. A CT scan and sestamibi scintigraphy are avoided, due to radiation risk to fetus. MRI neck is safe and can be used for localization, but lacks sensitivity for smaller adenomas. USG-guided fine-needle aspirate of the lesion along with PTH measurement in the aspirate has nearly 100% accuracy, but result depends upon successful pre-localization. In our 3 patients, USG neck was successful in localizing adenoma, but in one

patient it could not be performed due to critical condition and death.

The treatment options for PHPT in pregnancy include conservative approach or surgery, latter being the first choice. The conservative treatment includes hydration with or without forced calciuresis, oral phosphates and low-calcium diet. Oral phosphate carries the high risk of calcium phosphate precipitation. The role of bisphosphonates and calcimimetics as medical therapy has not been proven safe. Bisphosphonates can cross placenta, so its use should be restricted to life-threatening hypercalcemia. Calcitonin can be used during pregnancy with caution, as it does not cross placenta. However, its use is limited by insufficient safety data and poor effectiveness. Schnatz et al. [6] claimed that asymptomatic patients with serum calcium < 11 mg/dl can be managed by conservative medical therapy. But, they require close monitoring for the risk of hypercalcemic crisis during and after the pregnancy. These therapies have shown significant reduction in maternal and fetal complications [4]. All our 4 patients were hydrated

Fig. 1 USG appearance of adenoma

with intravenous normal saline (0.9%) in hospital, and second patient was discharged during first trimester, with advice to take lot of oral fluid till surgery. Both bisphosphonates and calcitonin were used in 3rd patient, whereas calcitonin along with hydration helped to lower serum calcium in 4th patient.

Surgery, the only curative treatment, is treatment of choice in patients with PHPT. It is recommended when calcium levels are above 11 mg/dl [7]. Surgery during pregnancy increases both maternal and fetal risks. It is safely recommended during second trimester, as the risk of anesthesia induced preterm delivery is lowest and organogenesis is complete. Focused or minimally invasive parathyroidectomy (MIP) is the therapeutic gold standard in the management of PHPT in pregnancy. This technique has gained acceptance in terms of safety and effectiveness over last two decades. It is associated with short hospital stay and small scar and is recommended when adenoma is clearly localized preoperatively. The exceptions to this early surgery rule would be if the diagnosis is made near term, the mother is asymptomatic, and the fetus is healthy. MIP has a success rate around 95%, in experienced hands [8]. Kelly [7] compared surgery to other treatment methods and showed the incidence of neonatal complications 10% versus 37% and neonatal mortality 3% versus 16%, respectively. Surgery during first trimester should be avoided due to incomplete organogenesis and possible

Fig. 2 a Gross features. b Histopathologic features

teratogenicity of anesthetics. A third trimester surgery poses a risk of preterm delivery. Several reports have documented the safety of parathyroid surgery during third trimester [9]. The decision should be made on the basis of degree of hypercalcemia and symptoms, along with fetal development. This may be an option for patients who present late into their pregnancy. If the patient and fetus can be brought through to term safely, or if the pregnancy is unfortunately lost, surgery should be undertaken post-delivery to minimize the risk of future miscarriages. First 2 patients in our series were operated by MIP during early second trimester and 4th case during third trimester.

If localization fails, bilateral neck exploration (BNE) is advocated. The intra-operative PTH measurement is a useful adjunct during parathyroidectomy. By Miami criteria, a decrease in intra-operative PTH by 50% and more at 10 min post-excision indicates successful surgery [10].

Intra-operative PTH measurement facility is not available in our hospitals.

Conclusion

Primary hyperparathyroidism in pregnancy is a rare disorder. The symptoms are often non-specific. It may be associated with significant maternal and fetal morbidity and mortality. The causative lesion in most of the cases is parathyroid adenoma, which may be localized by USG neck. In cases of severe hypercalcemia due to parathyroid adenoma, if operated during second trimester, prognosis is optimal for both mother and fetus. Screening of PHPT is necessary in pregnant women with any clinical presentation associated with hypercalcemia.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

Ethical Standards For this type of manuscript, formal consent is not required.

Informed consent Informed consent was obtained from all patients and their attendants.

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