Primary hyperparathyroidism with vitamin D deficiency in third trimester of pregnancy

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Abstract: In pregnancy, the diagnosis of primary hyperparathyroidism (PHP) may be delayed due to physiological changes that occur during this period. The maternal related complications of PHP during pregnancy has been reported to be as high as 67%, whilst fetal complications up to 80% of cases.[1] The therapeutic gold standard and definitive treatment for PHP in pregnancy is minimally invasive parathyroidectomy in the second trimester. We report a case of a 22-year old primidgravida who underwent parathyroidectomy in the third trimester of her pregnancy for PHP with persistent hypercalcemia. She was also found to have Vitamin D deficiency which probably led to secondary hyperparathyroidism and made her hypercalcemia more apparent during pregnancy.

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Case Report

Our patient is a 22-year old primidgravida who was referred to our hospital at 32 weeks of pregnancy for persistent hypercalcemia. She was well before her pregnancy and did not have any medical illnesses prior to that. Her initial presentation was to a district hospital during the first trimester for vomiting which was attributed to hyperemesis gravidarum. She was noted to have hypokalemia then but unfortunately her calcium levels were not assessed. At 30 weeks period of gestation, she was admitted again for premature contraction secondary to urinary tract infection. During this admission, she was noted to have parathyroid related hypercalcemia with corrected serum calcium of 3.33 mmol/L and parathyroid hormone level of 52.1 pmol/L. Despite aggressive hydration she remained hypercalcemic and was then referred to our hospital for further management.

On further assessment, she was not taking any calcium supplements or other medications that may contribute to hypercalcemia, such as lithium. She did not have any previous history of fracture or any symptoms of hypercalcemia (while on hydration). She was not aware of any family history of hypercalcemia or renal stones. Her blood pressure was 117/84 mm Hg with pulse rate of 84 beats per minute. Her voice was not hoarse and there was no palpable neck swelling or cervical lymphadenopathy. Per abdomen her uterus size corresponded to the period of gestation.

Biochemical evaluation revealed severe hypercalcemia with corrected calcium levels of 3.71 mmol/L and low phosphate of 0.61mmol/l. Her potassium level was 4.2 mmol/L while on supplements but blood gas showed metabolic acidosis with serum pH of 7.32 and HCO3 of 11.7 mmol/L which was due to nephrocalcinosis related renal tubular acidosis. The Total 25-hydroxy vitamin D level was noted to be low; 19.15 nmol/L. Her serial calcium/phosphate levels and other baseline investigations are as shown in Tables 1 and 2 respectively. Ultrasound of the neck showed hypoechoiec, enlarged parathyroid gland which was seen posterior to the left thyroid. It measured 2.3 cm x 1.3 cm. Ultrasound of kidneys showed bilateral nephrocalcinosis with no evidence of obstructive uropathy.

She was initially treated conservatively with aggressive hydration of up to 4 liters of normal saline per day with potassium supplements as well as subcutaneous calcitonin. Unfortunately her calcium levels remained elevated. In view of her persistent hypercalcemia and recent history of premature contraction, left superior and inferior parathyroidectomy as well as left hemithyroidectomy was done. Intraoperatively, enlarged left inferior parathyroid gland measuring 5x3 cm and left superior parathyroid gland measuring 6x7 mm were removed. Post operatively her calcium levels reduced gradually and was normal two weeks post surgery. Histopathology report showed nodular hyperplasia of left thyroid gland. (Figures 1 and 2). Figures 3 and 4 are sections from the left parathyroid gland which showed parathyroid adenoma.

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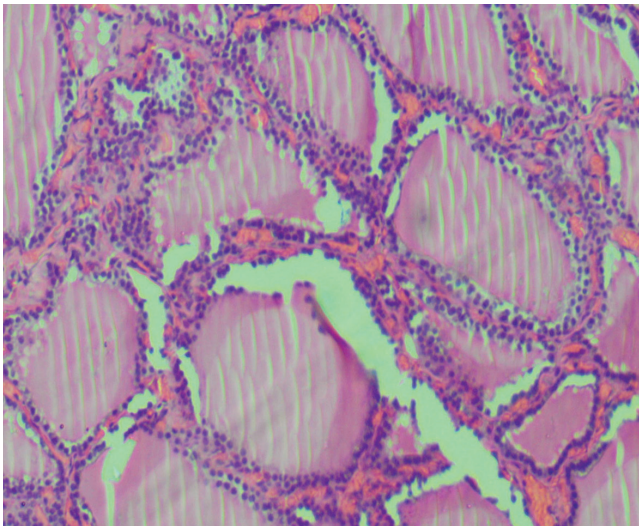

Figure 1 : (400X magnification)

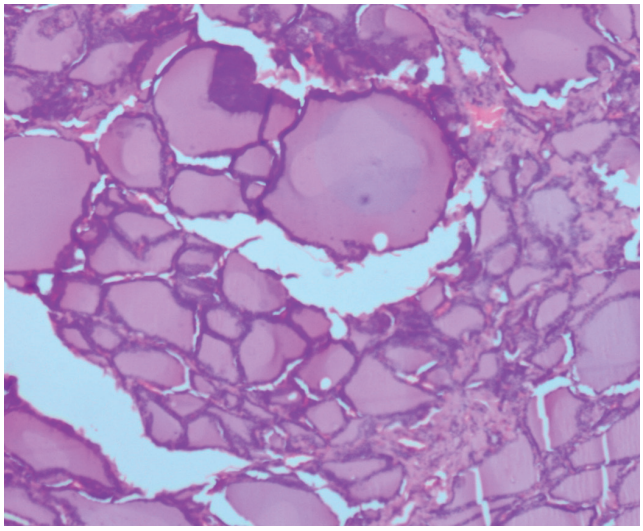

Figure 2: (400X magnification)

Figures 1 and 2: Sections from the left thyroid nodules composed of follicles of varying sizes filled with colloid. The follicles are lined by low columnar to cuboidal epithelium, few are exhibiting peripheral vacuolations. There is no evidence of malignancy seen.

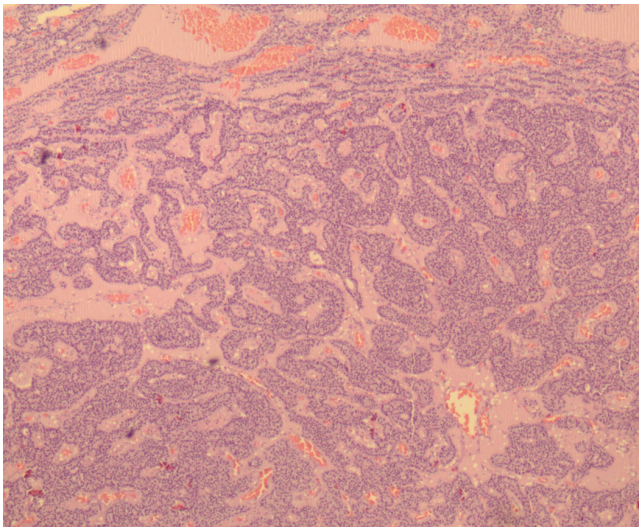

Figure 3: (100X magnification)

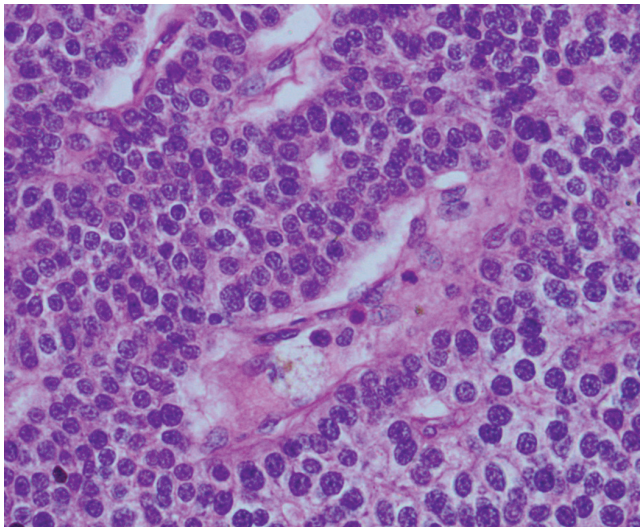

Figure 4: (400X magnification)

Figures 3 and 4: Sections showing cellular lesions. The cells are predominantly composed of chief cells arranged in solid sheets as well as micro-follicular pattern. Areas of hemorrhage with collections of hemosiderin-laden macrophages are also noted. There is no cellular atypia or evidence of malignancy seen.

The prevalence of PHP is reported to be 0.15% among general population but estimated to be as high as 1.4% if undiscovered cases are being taking into account.[2] In pregnancy, the true incidence of PHP is unknown since many cases remain asymptomatic. Some of the symptoms caused by hypercalcemia are also variable, vague and maybe wrongly be attributed to pregnancy related symptoms such as hyperemesis gravidarum. For instance in our patient, her vomiting was initially thought to be due to hyperemesis gravidarum and urinary tract infection.

Physiological changes in pregnancy in terms of calcium homeostasis may also mask the presence of hypercalcemia. These changes include intravascular fluid expansion leading to hemodilution, increase in glomerular filtration rate leading to hypercalciuria and gestational hypoalbuminemia. Maternal shunting of calcium to the fetus may contribute to a relative maternal hypocalcemia but the reduction in total maternal serum calcium levels observed during pregnancy is mainly the reflection of a decrease in serum albumin levels and consequently, a decrease in the albumin-bound fraction of calcium; the ionized calcium levels remain in the normal range during pregnancy.[3] It is therefore important to correct for lower albumin when evaluating calcium levels during pregnancies.

1,25-dihydroxyvitamin D plays a major role in maternal adaptation to provide for the fetal calcium demand. It is the main stimulus for increased intestinal calcium absorption. The level of 1,25 dihydroxyvitamin D rises during the pregnancy. Free 1,25-dihidroxyvitamin D and total serum 25-hydroxyvitamin D are also elevated. The conversion of 25-hydroxyvitamin D to its active form 1,25-dihydroxyvitamin D during pregnancy is increased by PTH-independent up-regulation of 1-alpha-hydroxylase in the maternal kidneys as well as other sources such as placenta, deciduas and fetal kidneys.[3] The paradoxical decrease in parathyroid hormone (PTH) during gestation is likely due to direct inhibition of high 1,25-dihydroxyvitamin D or by increased intestinal absorption of calcium.

Generally patients with PHP are often asymptomatic or they may have generalized non specific complaints that are consistent with their levels of calcium. The patients may not have any symptoms if their calcium levels are mildly elevated ie. less than 3 mmol/l. Those who have moderate elevation of calcium levels between 3-3.5 mmol/l may have more profound symptoms such as anorexia, nausea, vomiting and constipation. Levels that are even higher can manifest as renal impairment, mental status change and cardiac arrhythmia. Very severe hypercalcemia with calcium levels of more than 4.5 mmol/l can present with hypercalcemic crisis resulting in uremia, coma, cardiac arrest and even death.

Our patient who had PTH related hypercalcemia with concurrent Vitamin D deficiency was completely asymptomatic prior to pregnancy. Her low Vitamin D levels probably contributed to some degree of secondary hyperparathyroidism particularly when she was pregnant. This further increased her calcium levels and made her symptoms apparent (Tables 1 and 2).

Table 1: Calcium and Phosphate (PO4) results pre- and post-operatively

Parameters	Pre-op Baseline	Pre-op with Calcitonin and Hydration	Post-op Day 1	Post-op 2 weeks
Calcium (mmol/l)	3.35	3.09	2.51	1.62
Corrected calcium (mmol/l)	3.77	3.53	3.01	2.06
PO4 (mmol/l)	0.61	0.70	0.57	-
Albumin (g/dl)	19	18	15	18

Table 2: Other baseline investigations

Baseline Biochemical Parameters	Results
Urea (mmol/l)	2.0
Sodium (mmol/l)	131
Potassium (mmol/l)	4.2
Creatinine (ummol/l)	67
Magnesium (mmol/l)	0.76
Chloride (mmol/l)	108
T4 (pmol/l)	13.7
TSH (miu/l)	0.291
Total 25-hydroxyvitamin D (nmol/l)	19.15
IPTH (pmol/l)	52.1
Blood pH	7.32
Bicarbonate (mmhg)	11.7
Anion gap	15.5
Urine pH	7

During pregnancy, PHP have been reported to be associated with maternal complications up to 67% of cases and fetal complications up to 80% of cases.[2] Maternal complications include nephrolithiasis (which our patient has), radiographic bone disease, pancreatitis, hyperemesis gravidarum, muscle weakness, confusion and hypercalcemic crisis. A hypercalcemic crisis can also occur in the early post partum period due to the sudden interruption of the transplacental shunting of calcium from mother to fetus. PHP is also a disease which has been associated with endothelial damage, insulin resistance and cardiovascular disorders. Parathyroid adenoma even prior to delivery has been found to be associated with preeclampsia.[5] This is important particularly for our young patient and her future pregnancies. Fetal complications include neonatal tetany, still birth, miscarriage, premature birth, intrauterine growth retardation, low birth weight, transient hypocalcemia or even fetal demise.

Biochemical diagnostic work-up for PHP in a pregnant patient is similar to a non pregnant patient. A finding of elevated calcium level with low phosphate and detectable or elevated PTH supports the diagnosis of PTH. Evaluation of urinary calcium excretion is important to exclude familial hypocalciuric hypercalcemia (FHH) particularly in a setting of mildly elevated calcium levels with high/normal PTH and a

normal serum 25 hydroxyvitamin D level. FHH is not likely in our patient as she had moderately elevated calcium levels and already had complications of PHP i.e. nephrocalcinosis. Another interesting finding in our patient is the presence of metabolic acidosis with normal anion gap and hypokalemia. With a urine pH of 7, the most likely explanation is renal tubular acidosis. Hypercalciuria in PHP can lead to nephrocalcinosis and renal tubular dysfunction, which manifests as distal RTA.[4]

In terms of localisation studies, ultrasonography of the neck is the investigation of choice in pregnancy. The commonest cause of PHP in pregnancy is a single parathyroid adenoma, which represents 85% of all cases followed by 10% from primary parathyroid hyperplasia, 3% from multiple adenomas and 2% from parathyroid carcinoma.[1] Ultrasonography has a 69% sensitivity and 94% specificity in diagnosing a parathyroid adenoma.[2] Computerized tomography and seistamibi scintigraphy are contraindicated during pregnancy due to the possible risks of ionizing radiation to the fetus but MRI of the neck can be safely used during pregnancy.

The definitive management of PHP is surgical. In pregnancy, management of PHP depends on presence of symptoms (and severity), gestational age and patient's preference. In patients with asymptomatic mild hypercalcemia, a conservative management may be reasonable. This includes eucalcemic diet with hydration, furosemide and calcitonin. For symptomatic patients or those with calcium levels of 3mmol/l and above, immediate hospitalization with aggressive hydration and assessment of fetal well being is required. Hemodialysis is another modality of treatment for severe or refractory hypercalcemia. If all medical measures fail, parathyroidectomy is to be considered regardless of fetal gestation.

A minimally invasive parathyroidectomy during the second trimester is the therapeutic gold standard and the most definitive strategy in a patient with PHP in pregnancy. This is because during the second trimester, organogenesis is already complete and risk of preterm birth due to anaesthesia is lower. In our patient, parathyroidectomy was carried in the third trimester in view of persistent hypercalcemia above 3 mmol/l which did not improve with medical therapy.

This case underscores the importance of evaluating other causes of vomiting in pregnancy particularly if it is associated with other electrolyte abnormalities such as hypokalemia. Parathyroidectomy is a treatment of choice even in third trimester if conservative and medical therapy fail.

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