Primary Hyperparathyroidism in Pregnancy - a review

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Introduction

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 Though Primary hyperparathyroidism is considered rare in pregnancy, and only about 110 cases have so far been reported in world literature this is probably a considerable underestimate of its prevalence in patients. Due to the pregnancy changes of the hormonal milieu, mild elevations of PTH and calcium can result in levels within normal range and may go unnoticed by the clinician. The diagnosis is thus more fortuitous as our case below demonstrates.

Is this Hyperemesis Gravidarum?

A 32 yr old lady presented to Heatherwood hospital in Ascot at 8 weeks pregnancy with a 4 day history of nausea and vomiting. This was her second pregnancy having delivered vaginally a live female infant 7 yrs ago. Interestingly she had not suffered any problems in her first pregnancy.

At the time of presentation she was unable to tolerate any food and drink and was ketotic. An examination revealed evidence of dehydration. No neuro-deficit was seen. Clinical examination of the patient was otherwise unremarkable.

There was no history of any other problems and she have a history of being reasonably healthy throughout pregnancy. She was a non-smoker and gave a history of only social alcohol intake.

An ultrasound scan done immediately revealed the presence of a single IU gestational sac which corresponded to her dates.

A provisional diagnosis of hyperemesis gravidarum was made and the patient was admitted for IV hydration, antiemetics, and thiamine.

U&Es, TFTs, FBC were sent and this revealed a mild metabolic acidosis and elevated alkaline phosphate. The hematocrit was normal.

One week after admission she still continued to be symptomatic and by this stage had lost about 2 stones (more than 15% of her admission weight) body weight. She was still thirsty, constipated and felt very tremulous. Her urine output was adequate and there was no suggestion of any fluid and electrolyte imbalance.

We repeated all the bloods and included a calcium and phosphate levels as well. Surprisingly the calcium level was elevated at 3.56 mmol/l (normal values 2.02-2.06) with a low phosphate at 0.53 mmol/l (n- 0.8-1.45). In view of these results a serum PTH was obtained and this was found to be elevated at 10.2 pmol (normal 1.2 -6.9).

A diagnosis of primary hyperparathyroidism was then made and the patient underwent an ultrasound scan of the neck. This revealed a 0.5 cm hypoechogenic lesion dorsal to the left lobe of the thyroid. A MRI scan of the neck confirmed the findings suggesting the presence of a solitary parathyroid adenoma. She subsequently underwent a para-thyroidectomy at Hammersmith Hospital.
and made an uneventful recovery. Her post-operative calcium dropped to 2. She did well and had an uneventful antenatal course thereafter ultimately delivering a healthy female baby vaginally at T+10 gestation.

Discussion

Pregnancy and Calcium Metabolism:

There are marked changes in calcium homeostasis in pregnancy. Maternal serum calcium falls by about 10% in pregnancy. However as the serum albumin falls by about 20% the ionized calcium remains unchanged to exert its physiological effect. There is an active transport of calcium across the placenta and the fetal serum calcium (total and ionized) are higher than the maternal. There is also increased maternal absorption of calcium (150mg -400mg daily) and an increased maternal urinary excretion from 90-300 mg daily.

Parathyriod hormone is a 84 long sequence which stimulates bone resorption , renal tubular absorption and synthesis of calcitriol in the kidneys. There is a negative feedback loop with ionized calcium and calcitriol.

Serum conc. of PTH falls by 40% in 1st trimester and it does not cross the placenta. PTH related protein (PTHrp) is another calcium regulating hormone which binds to and activates PTH receptors. This is expressed in the uterus , placenta amnion umbilical cord, lactating breast and fetal parathyroid glands. This regulates calcium transport across placenta and is necessary for normal fetal skeletal development. It is elevated in pregnancy and lactation.

Calcitonin is another major player in calcium metabolism. It is a peptide hormone secreted by the parafollicular C cells of the thyroid and it inhibits bone resorption thereby lowering serum calcium. Its level do not change in pregnancy.

The active metabolite of Vit D 1,25 di- hydroxycholecalciferol is produced from the kidneys and is stimulated by PTH and decreased phosphate levels . It stimulates absorption of dietary calcium and rises early in pregnancy and stays elevated throughout. It does cross the placenta and also stimulates the production of human placental lactogen (HPL).

Primary hyperparathyroidism:

Hyperparathyroidism represents an excessive secretion of PTH ands may be primary and secondary. It is 2 -3 times more common in females than in males. The annual incidence rises with age and is uncommon before 40. Only 110 cases in pregnancy has so far been reported in pregnancy but this probably represents an under diagnosis as no diagnostic algorithms are in place for this condition. Instead, diagnosis relies purely on clinical suspicion.

Primary hyperparathyroidism usually arises out of a single parathyroid adenoma in 90% of cases , multiglandular hyperplasias in about 8-10% of cases and carcinomas in about 1-2% of cases. A similar distribution exists in pregnancy as well. The finding of multiple adenomas during surgery should prompt familial screening studies in search for multiple endocrine neoplasia types 1 and 2A, familial hyperparathyroidism and familial hypocalciuric hypercalcemia. It is carcinomatous in about 1% of cases. In some patients gene mutations have been identified but the etiology remains mostly unknown. Rarely might it rise from an ectopic PTH secretion notably small cell carcinoma of the lungs.

Clinical features:

Most cases are asymptomatic(60%). Common clinical presentations are of fatigue, weakness, GI symptoms, nausea and vomiting, polyuria, thirst, weight loss and hypertension. In 6 % of pregnant cases it might be associated with pancreatitis when the maternal and foetal mortality and morbidity are considerably higher. X rays reveal the presence of radiolucent bone cysts (osteitis fibrosa cystica). In the postpartum period hypercalcemic crises can develop resulting in coma and death.

Neonatal effects are titan and death about 80% of cases. Thirty percent (30%) of affected infants may demonstrate transient neonatal hypocalcemic tetany. It is also associated with a 15% risk of spontaneous miscarriage in early pregnancy.
The diagnosis of this condition is mainly that of exclusion.

Important biochemical features are:

- Hypercalcemia
- Elevated PTH
- Hypophosphatemia
- Hypochloremic Metabolic Acidosis
- Elevated Serum Alkaline Phosphatase
- Elevated Serum Calcitriol

One must keep in mind the normal values of the above in pregnancy and should verify the levels with a second sample to rule out laboratory error. Other causes of hypercalcemia like excessive ingestion of calcium and vit D, thiazide diuretics, lithium therapy, sarcoidosis and haemoconcentration must be ruled out.

**Management:**

Patients can be treated conservatively in pregnancy but this approach is considered risky by most authors as there is a high frequency of foetal loss. Medical treatment can be instituted with oral elemental phosphate 1.5-2 g/day and rehydration this is especially beneficial in an emergency to bring the serum calcium down to prevent tetanic spasms.

However surgery in the form of parathyroidectomy remains the standard form of therapy in pregnancy.

Hypercalcemic crises can be treated with saline diuresis, calcitonin and inorganic phosphate. Frusemide, mithramycin, biphosphonates, and gallium though standard treatment medically are considered unsafe in pregnancy.

When hyperparathyroidism is diagnosed, the family history should be reviewed and the ratio of urinary calcium clearance to creatinine clearance should be determined, to exclude familial hypocalciuric hypercalcemia.

For a woman with asymptomatic or mild primary hyperparathyroidism, who is contemplating pregnancy preconception surgical treatment remains the best option. This avoids unnecessary neck exploration during pregnancy. At a minimum the possible problems associated with hyperparathyroidism in pregnancy must be discussed. In addition should the patient belong to one of the heritable syndromes associated with this condition genetic counselling must be sought. DNA based screening tests on the peripheral blood are available which can now identify MEN 2 syndromes.

**References:**


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