Recurrent Pregnancy Induced Hypercalcaemia Resulting in Multiple Terminations of Pregnancy

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Introduction

- Pregnancy is characterized by increased intestinal calcium absorption, normal ionized or albumin-corrected calcium, high calcitriol, low parathyroid hormone (PTH), gradually increasing PTH related peptide (PTHrP), and hypercalciuria (Fig. 1).
- These differing hormonal changes can lead to nonclassic presentations of disorders of bone and mineral metabolism.

Hypercalcaemia in Pregnancy

- Normal pregnancy is associated with many nonspecific symptoms that overlap with symptoms of hypercalcaemia, such as nausea, hyperemesis, constipation, fatigue, weakness, and mental symptoms.
- The overlap of symptoms may delay the diagnosis of hypercalcaemia and/or hyperparathyroidism.
- Stillbirth, miscarriage, and neonatal tetany remain among the serious and common complications of hypercalcaemia. Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcaemia in pregnancy.

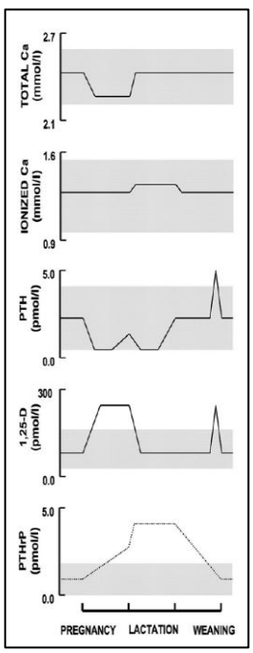

Figure 1. The longitudinal changes in calcium and calcitropic hormone levels that occur during pregnancy and lactation. Normal adult ranges are indicated by the shaded areas.

Treatment Goals

- Medical treatment includes adequate hydration and correction of electrolyte abnormalities, but pharmacologic agents approved to treat hypercalcaemia have not been adequately studied in pregnancy.
- In PHPT, localizing an adenoma preoperatively is difficult because the radioisotopes needed for parathyroid and thyroid scans must be avoided, ultrasonography has limited sensitivity.
- In the postpartum interval the serum calcium should be expected to increase after the placenta is discharged and as the haemodilution of pregnancy resolves.
- Neonatal hypocalcemia and other complications are not inevitable after marked maternal hypercalcemia during pregnancy.

Case Report

PRESENTATION:

A first-trimester 34 year old multigravida patient presented with hyperemesis, abdominal pain, polyuria, polydipsia, leg cramps and constipation.

Hypercalcaemia (4.13mmol/L) with suppressed PTH was found (Fig. 2). She denied taking any exogenous calcium. 25OH-VitD was low (40nmol/L) and angiotensin converting enzyme (ACE) levels were normal. 24hr urinary calcium and serum1,25OH-VitD were elevated. PTHrP was variably elevated which may be related to the reliability of the assay itself.

Imaging of breast, abdomen and thorax, revealed no evidence of maternal malignancy. Bone mineral density at the hip revealed a T-score of -1.7 and a Z score -1.5 whilst the lumbar spine was normal.

Management & Subsequent Pregnancies

Intravenous fluid therapy led to short lived symptomatic improvement. Short course of prednisolone failed to suppress serum calcium.

Safety of bisphosphonates during pregnancy is not established. Decision was made for medical termination of pregnancy (TOP) at 17 weeks from lack of symptomatic control of hypercalcaemia and the concern of its effect on the foetus.

Calcium, PTHrP and 1,25OH-VitD levels normalised post termination. Foetal autopsy revealed no abnormalities apart from placental membrane calcification. The risks of gestational hypercalcaemia in future pregnancies discussed and advised earlier monitoring of calcium.

She conceived again and developed hypercalcaemia, elevated 1,25OH-VitD and variably elevated PTHrP. Hypercalcaemia was uncontrolled, requiring termination (12 weeks) with subsequent normalisation of calcium metabolic parameters. Placental analysis failed to show abnormal PTHrP staining.

Extensive counselling undertaken regarding future pregnancies. There was no hypercalcaemia in previous pregnancies with former partner.

The patient and her current partner keen to pursue further pregnancy. In 2008, she conceived again with a miscarriage at 8 weeks. She had another TOP in 2013 due to gestational hypercalcaemia.

The usual causes of hypercalcaemia were excluded. This appears to be a pregnancy-related phenomenon, and postulated mechanisms are either excessive calcium gut absorption due to increased sensitivity to 1,25 Vitamin D or an occult source.

There are currently limited studies assessing the role of bisphosphonates in pregnancy or other potential calcium lowering therapies (e.g. denosumab).

Trend of Calcium

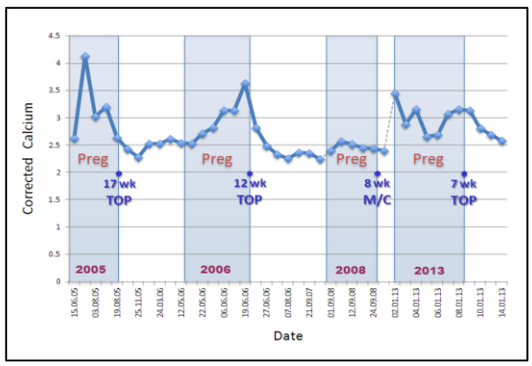

Figure 2. Trend of calcium during successive pregnancies.

Discussion

This is a case of recurrent severe gestational hypercalcaemia that develops early in pregnancy after 3 successful pregnancies with a previous partner.

The underlying pathogenesis is not known. There is also limited literature to describe or manage this phenomenon.

PTHrP was variably elevated in the first event, but was not consistently elevated in the subsequent pregnancies, such that its role in this is unclear.

1,25-OH VitD was consistently elevated suggesting possibility of increased placental 1-α hydroxylase enzyme activation.

Aberrant prolactin receptors and its responsiveness to physiological levels of prolactin may increase PTH with altered gene transcriprition.

The role of bisphosphonate or denosumab for hypercalcaemia in such circumstances needs further research. Her calcium homeostasis returns to normality immediately post termination.

References

• Kovacs CS. Calcium and bone metabolism disorders during pregnancy and lactation. Endocrinol Metab Clin N Am 40 (2011) 795-826.
• Mastaglia SR, et al. Intravenous bisphosphonate treatment and pregnancy: its effects on mother and bone health. Osteoporosis Int (2010).
• Levy S, et al. Pregnancy outcome following utero exposure to bisphosphonate. Bone (2009).
• Ornoy A, et al. The outcome of pregnancy following pre-pregnancy or early pregnancy alendronate treatment. Reprod Toxicol (2006) 578–579.