Severe hypercalcaemia during pregnancy is rare and most cases are secondary to hyperparathyroidism. This is the first report of a parathyroid hormone related protein (PTHrP) secreting neuroendocrine tumour of the pancreas manifesting with severe hypercalcaemia during pregnancy. Measurement of PTHrP was useful in both the diagnosis and follow up of our patient and should be considered in the diagnostic workup of patients with unexplained hypercalcaemia. A raised PTHrP concentration is a strong indicator of malignancy.

Severe hypercalcaemia during pregnancy is rare and most cases are due to hyperparathyroidism but there are fewer than 150 patients reported in world literature. There have been two reports of the milk alkali syndrome and four reported cases of parathyroid carcinoma during pregnancy. Other cases of malignancy related hypercalcaemia in pregnancy are very rare. Parathyroid hormone related protein (PTHrP) was first isolated in 1987 from cancer cell lines and a tumour associated with hypercalcaemia, and is now considered to be the main mediator of humoral hypercalcaemia of malignancy. The placenta (during pregnancy) and mammary glands (postpartum) are important physiological sources of PTHrP.

We report a case of extreme hypercalcaemia manifesting during pregnancy. The hypercalcaemia was associated with raised levels of 1,25-dihydroxyvitamin D$_3$ and was eventually found to be due to a PTHrP secreting neuroendocrine tumour.

### CASE REPORT

A 25 year old woman presented at 29 weeks' gestation with altered consciousness, headache, hypertension and proteinuria, and was initially thought to have pre-eclampsia. She was noted to have taken 1 g of mefenamic acid in divided doses during the two days before presentation.

Her initial investigations showed a serum calcium adjusted for albumin of 5.9 mmol/l (reference range 2.2–2.6). A retrospective measurement of calcium at 19 weeks' gestation was obtained at 2.33 mmol/l. Her serum phosphate was raised at 2.07 mmol/l (reference range 0.7–1.2), probably as a result of her renal impairment. She had renal failure with a serum creatinine of 328 µmol/l (reference range 60–110) and her 24 hour urinary protein was 9.09 g. Parathyroid hormone was undetectable using a two site immunoradiometric assay (Diagnostic Product Corporation Immulite, Los Angeles USA).

**Abbreviations:** 1,25(OH)$_2$D$_3$, 1,25-dihydroxyvitamin D$_3$, 25(OH)D$_3$, 25-hydroxyvitamin D$_3$, PTHrP, parathyroid hormone related protein
uptake in the region of the distal pancreas with no evidence of metastases.

A vitamin D challenge test was performed by administering 2000 IU of 25(OH)D₃ for 10 days with alternate day measurement of calcium and vitamin D metabolites (see table 1). This suggested inappropriate activation of vitamin D since the levels of 1,25(OH)₂D₃ remained suppressed, consistent with a hyperparathyroidism stimulating effect of PTHrP on 1α-hydroxylase activity. In keeping with this hypothesis, serum 1,25(OH)₂D₃ levels were increased in various animal models of PTHrP mediated humoral hypercalcaemia of malignancy. Reasons that have been put forward to explain the lower levels of 1,25(OH)₂D₃ in humoral hypercalcaemia of malignancy compared with primary hyperparathyroidism include the fact that humoral hypercalcaemia of malignancy is often associated with very severe hypercalcaemia and renal failure which can suppress 1α-hydroxylase activity and that many patients with humoral hypercalcaemia of malignancy have low levels of the precursor 25(OH)₂D₃. Inappropriate activation of 1,25(OH)₂D₃ production was found in our patient, which almost certainly represented a stimulatory effect of PTHrP on renal 1α-hydroxylase activity.

The reduction in PTHrP and calcium after administration of somatostatin analogue octreotide is interesting and has been documented previously in other neuroendocrine tumours. This may have therapeutic potential if surgical clearance is not possible. PTHrP measurements were useful in this case in clarifying the diagnosis of the hypercalcaemia and in follow-up as the PTHrP remained reassuringly normal over two years of follow-up. PTHrP measurement should be considered in the diagnostic workup of hypercalcaemia of obscure aetiology. A raised PTHrP concentration is strong evidence for the presence of malignancy.

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The PTHrP was measured at the Department of Clinical Chemistry, Royal Liver Hospital.

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P Abraham, S H Ralston, M Hewison, W D Fraser and J S Bevan

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