Hypercalcaemia in Pregnancy

Three Distinct Case Presentations, Aetiologies and Acute Management Strategies for this Rare Condition

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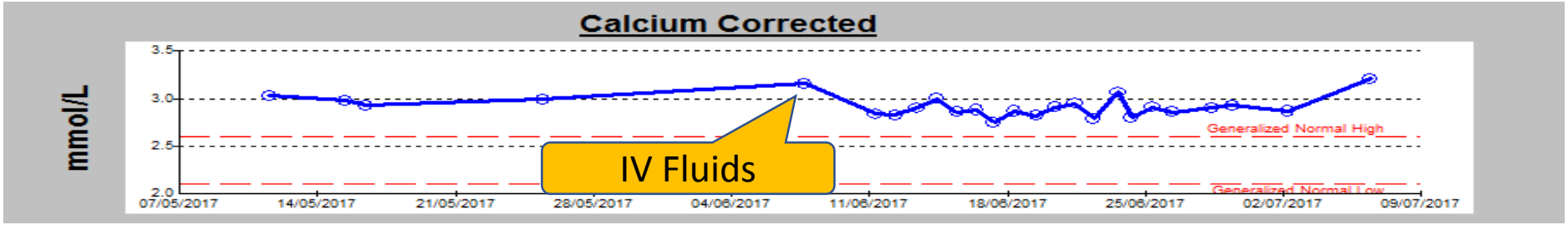
Case 1: Mrs BV

- 30 year old lady, G1P0, 33/40
- Asymptomatic hypercalcaemia (3.03mmol/L)
- Medical Background:
  - Primary Hyperparathyroidism (2010)
  - Complications: nephrolithiasis, fatigue, abdominal bloating, low BMD
  - Neck exploration 2010: unable to localise

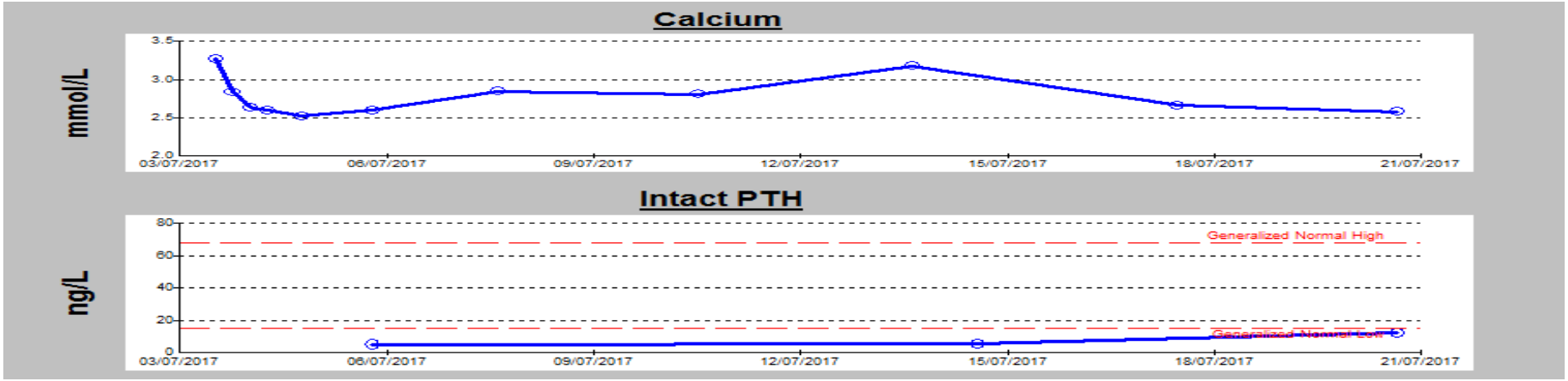
Test	Result
Ca	3.03 mmol/L
PTH	15.9pmol
Vitamin D	88nmol/L
Urinary Ca	14mmol/d
US neck	1cm nodule below right lower pole

Case 1: Mrs BV

Maternal Calcium Levels



Neonatal Calcium and PTH levels



Complications of Hypercalcaemia in Pregnancy

Maternal Complications	Foetal Complications
Severe hypertension Pancreatitis Nephrolithiasis Renal insufficiency	IUGR Foetal Death in Utero Neonatal death Neonatal hypocalcaemia with tetany Permanent hypoparathyroidism -rare

Rey E, Jacob C, Koolian M, Morin F. *Clinical Case Reports*. 2016;4(10):1001-1008. doi:10.1002/ccr3.646.

Case 2: Mrs CH

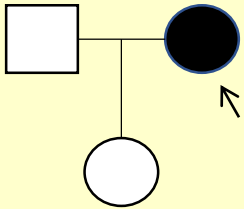
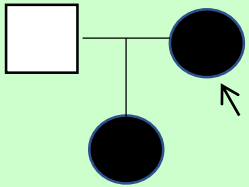
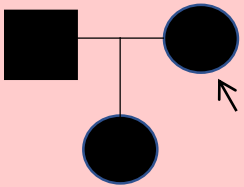
- 34 year old lady, G1P0, IVF pregnancy
- Asymptomatic Hypercalcaemia (2.6mmol/L)

- Medical Background:
  - Suspected Familial Hypocalciuric Hypercalcaemia (FHH)
  - Persistent Hypercalcaemia after parathyroidectomy
- Genetic testing: Heterozygous missense mutation at Calcium sensing receptor (CaSR) → Benign condition

- Managed expectantly

- Baby of Mrs CH elevated calcium (Ca2.92mmol/L), likely inheritance

Foetal Outcomes of FHH in Pregnancy

'Normal' CaSR	Heterozygous CaSR mutation	Homozygous CaSR mutation
		
Unaffected foetus exposed to hypercalcaemia may have suppressed parathyroid gland development in utero Risks: • IUGR • neonatal hypocalcaemia • seizures and tetany • FDIU	50% of foetuses will inherit the CaSR mutation Autosomal dominant Asymptomatic hypercalcaemia	Autosomal recessive (compound heterozygous or homozygous) Severe neonatal hypercalcaemia Bone radiographs may reveal marked demineralization and subperiosteal resorption with multiple fractures

Case 3: Mrs EL

- 33 year old lady
- G3P2, 29+1/40
- Presented with back pain, severely reduced mobility
- Medical Background:
  - Known BRCA 2 positive mutation
  - Bilateral mastectomy 2012 following DCIS, annual surveillance
- MRI spine: Multiple metastatic lesions in spine with pathological fractures

Ca	PTH	Vitamin D	PTHrP
3.36 mmol	<4.0pmol	75mmol	2.1pmol

- Commenced on calcitonin 100units TDS and aggressive IV fluids

Acute Medical Management of Hypercalcaemia in Pregnancy

Therapy	Mechanism of action	Use in pregnancy
IV fluids	Correction of volume depletion due to hypercalcaemia induced urinary salt wasting	First line therapy
Calcitonin	Decreases hypercalcaemia by inhibiting osteoclast activity → inhibits bone resorption and enhances renal excretion of calcium	Safe, does not cross placenta Tachyphylaxis limits efficacy
Bisphosphonate	Inhibit bone resorption, decrease calcium release → decrease serum calcium	Retained in skeleton, cross the placenta, teratogenic
Cinacalcet	Calcimimetic binding to CaSR→ decrease PTH secretion	CaSR present on placenta, lack of data in pregnancy
Surgery	Resection of adenoma in PHPT	Early in second trimester

...Acknowledgements

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Mrs BV, Mrs CH, Mrs EL

…Questions?

Calcium Physiology in Pregnancy

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)
- hypercalciuria

Measured levels	Pregnant woman	Placenta	Fetus	Lactating woman
Serum Ca	Total Ca ↓ Ionized Ca↔ Intestinal absorption twofold ↑	Active transfer dependent on PTHrP + passive transfer	Higher than maternal levels; regulated by fetal PTHrP	Ionized Ca slightly ↑ Bone resorption ↑
Urinary Ca	↑		Unknown	↔
PTH	↓↔	No transfer	Low	Low
PTHrP	Progressively ↑ secretion by decidua and breasts	No transfer; placental and amniotic secretion	Higher than in mother Secretion by the umbilical cord and fetal parathyroid glands as early as 10 weeks	↑↑: secretion by breasts
25-vitamin D	↔	Transfer; placental hydroxylation	Renal hydroxylation	↔
1,25-dihydroxyvitamin D	Progressive ↑ by 100%; calbindin-D9k ↑ ↑	No transfer	Low	↔
1α-hydroxylase activity	Stimulated by estradiol, prolactin, placental lactogen, PTHrP	Present	Present in the kidney	↔

Foetal Complication Rates

Foetal:

- IUGR
- Early or late demise (2 - 30%)
- Neonatal death (2%)
- Neonatal hypocalcaemia with tetany (15- 50%)
- Permanent hypoparathyroidism -rare

Urinary Calcium

- Pregnancy is associated with an increase in creatinine clearance and glomerular filtration rate
- The 24-h urine calcium excretion is increased as early as the 12th week of gestation (the earliest time point studied), and averages 300 ± 61 mg in the third trimester (levels in the hypercalciuric range are not uncommon)
- no laboratory normal ranges

How high is too high?

- Maternal calcium levels under 2.85mmol/L seem to be associated with decreased risk of foetal adverse effects
  - Case reports of adverse effects at even mildly elevated Ca levels
- Non pregnant levels:
  - Any symptomatic hypercalcaemia
  - Mild: 2.5 - 3mmol/L – may not warrant immediate therapy
  - Moderate 3-3.5mmol/L – may warrant urgent therapy depending on symptoms
  - Severe >3.5mmol/L – warrants immediate therapy,

Screening?

- Hypercalcaemia in pregnancy is rare
- <1% of pregnancies affected
- Based on history and clinical suspision