Hypercalcaemia in Pregnancy

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

Dr Natassia Rodrigo

Research Fellow, Royal North Shore Hospital
Associate Clinical Lecturer, University of Sydney
Prospective PhD Candidate, University of Sydney
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

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>3.03 mmol/L</td>
</tr>
<tr>
<td>PTH</td>
<td>15.9 pmol</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>88 nmol/L</td>
</tr>
<tr>
<td>Urinary Ca</td>
<td>14 mmol/d</td>
</tr>
<tr>
<td>US neck</td>
<td>1 cm nodule below right lower pole</td>
</tr>
</tbody>
</table>
Case 1: Mrs BV

Maternal Calcium Levels

Neonatal Calcium and PTH levels
Complications of Hypercalcaemia in Pregnancy

<table>
<thead>
<tr>
<th>Maternal Complications</th>
<th>Foetal Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypertension</td>
<td>IUGR</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Foetal Death in Utero</td>
</tr>
<tr>
<td>Nephrolithiasia</td>
<td>Neonatal death</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Neonatal hypocalcaemia with tetany</td>
</tr>
<tr>
<td></td>
<td>Permanent hypoparathyroidism - rare</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>‘Normal’ CaSR</th>
<th>Heterozygous CaSR mutation</th>
<th>Homozygous CaSR mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.png" alt="Family Tree" /></td>
<td><img src="image.png" alt="Family Tree" /></td>
<td><img src="image.png" alt="Family Tree" /></td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th></th>
<th>Ca</th>
<th>PTH</th>
<th>Vitamin D</th>
<th>PTHrP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.36 mmol</td>
<td>&lt;4.0 pmol</td>
<td>75 mmol</td>
<td>2.1 pmol</td>
</tr>
</tbody>
</table>

- Commenced on calcitonin 100 units TDS and aggressive IV fluids
## Acute Medical Management of Hypercalcaemia in Pregnancy

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

Dr Sarah Glastras
Dr Samantha Hocking
Dr Rachel McGrath
Prof Rory Clifton Bligh
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
<table>
<thead>
<tr>
<th>Measured levels</th>
<th>Pregnant woman</th>
<th>Placenta</th>
<th>Fetus</th>
<th>Lactating woman</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca</td>
<td>Total Ca ↓</td>
<td>Active transfer dependent on PTHrP + passive transfer</td>
<td>Higher than maternal levels; regulated by fetal PTHrP</td>
<td>Ionized Ca slightly ↑ Bone resorption ↑</td>
</tr>
<tr>
<td>Urinary Ca</td>
<td>↑</td>
<td>No transfer</td>
<td>Unknown</td>
<td>⇐</td>
</tr>
<tr>
<td>PTH</td>
<td>↓ ⇐</td>
<td>No transfer; secretion by decidua and breasts</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>PTHrP</td>
<td>Progressively ↑ secretion by decidua and breasts</td>
<td>No transfer; placental and amniotic secretion</td>
<td>Higher than in mother Secretion by the umbilical cord and fetal parathyroid glands as early as 10 weeks</td>
<td>↑↑: secretion by breasts</td>
</tr>
<tr>
<td>25-vitamin D</td>
<td>⇐</td>
<td>Transfer; placental hydroxylation</td>
<td>Renal hydroxylation</td>
<td>⇐</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D</td>
<td>Progressive ↑ by 100%; calbindin-D9k ↑</td>
<td>No transfer</td>
<td>Low</td>
<td>⇐</td>
</tr>
<tr>
<td>1α-hydroxylase activity</td>
<td>Stimulated by estradiol, prolactin, placental lactogen, PTHrP</td>
<td>Present</td>
<td>Present in the kidney</td>
<td>⇐</td>
</tr>
</tbody>
</table>
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 suspicion