Maternal hypercalcaemia due to CYP24A1 loss of function mutations

Thomas Upton¹, Penny Hunt¹, Ian Phillips², Chris Florkowski², Martin Kaufmann³
¹Department of Endocrinology, Christchurch Hospital, New Zealand; ²Canterbury Health Laboratories, Christchurch, New Zealand, ³Department of Biomedical and Molecular Sciences, Queen’s University, Ontario, Canada

Introduction
• Changes in calcium homeostasis occur during normal pregnancy to meet the needs of the growing fetus
• These include marked rise in 1,25-dihydroxyvitamin D (1,25-(OH)₂D₃) and suppression of parathyroid hormone (PTH)
• However, maternal hypercalcaemia is very uncommon and should prompt further investigation

Case history
• A 24-year-old primigravida was diagnosed with hypercalcaemia from 6/40 gestation
• The pregnancy was otherwise uncomplicated and she delivered a healthy male infant at 38/40
• Hypercalcaemia resolved within 4 weeks postpartum, although hypercalciuria persisted

CYP24A1 mutations identified in the family
The asymptomatic younger brother of the index case (II-1) was identified during genetic screening

<table>
<thead>
<tr>
<th></th>
<th>Calcium (2.2-2.6 mmol/L)</th>
<th>PTH (1.6-7.0 pmol/L)</th>
<th>Urine Ca:Cr ratio (0.08-0.46)</th>
<th>25-OH-D₃ (58-150 nmol/L)</th>
<th>1,25-(OH)₂D₃ (65-175 pmol/L)</th>
<th>24,25-(OH)₂D₃ (nmol/L)</th>
<th>25-OH-D₂:24,25-(OH)₂D₃ ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/3</td>
<td>2.9</td>
<td>0.7</td>
<td>2.09</td>
<td>116</td>
<td>380</td>
<td>0.6</td>
<td>107</td>
</tr>
<tr>
<td>Post-partum</td>
<td>2.5</td>
<td>1.8</td>
<td>0.76</td>
<td>65</td>
<td>149</td>
<td>0.6</td>
<td>16</td>
</tr>
<tr>
<td>I-1</td>
<td>2.4</td>
<td>3.0</td>
<td>0.37</td>
<td>82</td>
<td></td>
<td>5.0</td>
<td>16</td>
</tr>
<tr>
<td>I-2</td>
<td>2.5</td>
<td>3.4</td>
<td>0.26</td>
<td>52</td>
<td></td>
<td>2.7</td>
<td>19</td>
</tr>
<tr>
<td>II-1</td>
<td>2.7</td>
<td>0.9</td>
<td>1.23</td>
<td>88</td>
<td>ULN</td>
<td>0.6</td>
<td>157</td>
</tr>
<tr>
<td>II-2</td>
<td>2.4</td>
<td>3.9</td>
<td>0.14</td>
<td>46</td>
<td></td>
<td>1.9</td>
<td>24</td>
</tr>
</tbody>
</table>

Learning points
• The differential diagnosis of hypercalcaemia in pregnancy should include disordered 1,25-(OH)₂D₃ metabolism caused by mutations in CYP24A1
• Other clinical manifestations include hypercalciuria, which may persist even when calcium is within the normal range
• Ratio of 25-OH-D₃:24,25-(OH)₂D₃ is significantly elevated in affected cases, predicting mutation status
• Vitamin D metabolite analysis is therefore a useful adjunct to genetic testing in suspected cases

References
http://doi.org/10.1210/jc.2013-4388

A model of vitamin D metabolism
• 1,25-(OH)₂D₃ (calcitriol) is metabolised by CYP24A1 encoded 24-hydroxylase to the inactive calcitroic acid (24,25-(OH)₂D₃)
• Mutations in CYP24A1 impair 24-hydroxylase activity resulting in reduced vitamin D metabolism, rises in 1,25-(OH)₂D₃, and increased susceptibility to hypercalcaemia

Figure reproduced from Schlingmann et al. NEJM 2011

Bone and calcium