Pregnancy and Sarcoidosis*

An Insight Into the Pathogenesis of Hypercalciuria

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Hypercalciuria with or without hypercalceemia is a well-known complication of sarcoidosis, the pathogenesis of which is not fully understood. Pregnancy is associated with physiologic alterations in calcium metabolism. These changes can further alter the derangement of calcium metabolism that occurs in sarcoidosis, if the two conditions coexist. We had the opportunity to study prospectively the changes in serum and urine calcium along with all the hormonal changes that occur during pregnancy in a young woman with sarcoidosis, who had hypercalciuria at presentation. We believe that an increased level of calcitriol is central to the calcium abnormalities in our patient. In her case, the increased calcitriol is derived from sarcoid granulomas and renal sources enhanced by the effect of estradiol and prolactin on the conversion of 25(OH)D to 1,25(OH)₂ D. She acquired hypoparathyroidism, with normal serum calcium, which probably was due to the direct suppression of parathyroid hormone (PTH) secretion by calcitriol. Finally, hypercalciuria is the result of the combined effect of hyperabsorption of calcium from the gut (the result of increased calcitriol levels leading to increased filtration of calcium) and decreased tubular reabsorption of calcium, as a result of undetectable PTH. (CHEST 2004; 126:995–998)

Key words: calcium metabolism; 1,25 dihydroxyvitamin D₃; hypercalciuria; pregnancy; sarcoidosis, parathyroid hormone

Abbreviations: ACE = angiotensin-converting enzyme; FSH = follicular stimulating hormone; iPTH = intact parathyroid hormone; LH = luteinizing hormone; PTH = parathyroid hormone

Disorders of calcium metabolism are common in sarcoidosis; of these, hypercalciuria is the most common, being present in 15 to 62% in various published series. Sarcoidosis commonly affects young adults. It has been observed that the clinical symptoms and the abnormalities in chest radiographic findings in patients with sarcoidosis frequently improve during pregnancy, and exacerbate again in the puerperium. In a retrospective study of sarcoidosis and pregnancy, Selroos found that, in 25 of his 38 patients, sarcoidosis was diagnosed for the first time within 1 year after delivery. However, O’Leary found that 79% of his 28 patients with sarcoidosis did not show clinical improvement during pregnancy.

During normal pregnancy, the body undergoes physiologic alterations in calcium metabolism in order to supply adequate calcium to the fetus and, at the same time, sustain normal blood and bone calcium levels in the mother. If pregnancy and sarcoidosis coexist, the physiologic changes in pregnancy can aggravate derangements of calcium metabolism that occur in sarcoidosis. We report a young woman with sarcoidosis in whom we carried out a prospective study of her serum and urine calcium, and of the relevant hormonal changes that occurred during pregnancy.

Case Report

This 33-year-old woman received a diagnosis of sarcoidosis 5 months after her first delivery. The diagnosis was based on a skin lesion biopsy and bilateral parenchymal lesions on chest radiograph. Except for the skin lesions, she had no other symptoms. Her mother also had sarcoidosis, which was detected after her second pregnancy, and resorted after a course of corticosteroids without further relapse. The present patient was referred to our service, because of severe hypercalcemia (24-h urine calcium, 17.2 mmol). Clinical examination was normal. She had normal serum creatinine and creatinine clearance, normal urinalysis, and no evidence of renal calculi. Because she was asymptomatic, she received no specific therapy other than the advice to take adequate oral fluids and to restrict her intake of dietary calcium. Over the following year, her chest radiographic findings became normal, and the urinary calcium excretion returned to normal range (Table 1). Three years later at the age of 37 years, she became pregnant again and agreed to cooperate in an investiga-
tion during and following her pregnancy. Her pregnancy and delivery were uneventful, and there were no neonatal complications. The baby’s weight was 6 lb, 6 oz, and he was healthy in all aspects. This article reports the results of these investigations, and attempts to explain the findings in the light of existing knowledge.

**Materials and Methods**

The ADVIA 1650 analyzer (Bayer Diagnostics; Bershire, UK) was used to estimate serum creatinine, calcium, albumin, urine creatinine, and urine calcium levels. The Jaffe reaction and enzymatic reaction of Tanganelli was used to measure urine creatinine, and urine calcium levels. The Doumas, Watson, and Biggs method using bromcresol green as the binding dye was used to estimate serum albumin. The reaction between calcium and o-cresolphthalein complex one was used to measure serum intact parathyroid hormone (iPTH) was estimated using a solid-phase, two-site, chemiluminescent enzyme-labeled immunometric assay in the Immulite (iPTH) was estimated using a solid-phase, two-site, chemiluminescent enzyme-labeled immunometric assay in the Immulite.

Serum 1,25 dihydroxyvitamin D was estimated by a competitive radioimmunoassay kit manufactured by DiaSorin. The vitamin D metabolites were extracted and purified using a DiaSorin 25 hydroxy vitamin D radioimmunoassay (DiaSorin; Stillwater, MN). Rate spectrophotometric method using reagents from Sigma Diagnostics (Columbia, MD) was used in the measurement of serum angiotensin-converting enzyme (ACE) levels. Serum 1,25 dihydroxyvitamin D was estimated by a competitive radioimmunoassay kit manufactured by DiaSorin.

The 1,25-dihydroxy vitamin D (calcitriol) level that was normal before pregnancy increased throughout pregnancy, and became normal soon after delivery only to rise again and remain high thereafter. Interestingly, her serum iPTH level that was at the lower levels of normal before pregnancy became undetectable throughout pregnancy and returned to baseline 2 years after delivery. Serum ionized calcium, phosphorous, albumin, creatinine and 25-hydroxycholecalciferol levels were normal and remained so throughout the pregnancy and puerperium. Serum ACE levels were in the high normal range during pregnancy and decreased after delivery. As expected, there was a progressive increase in the blood levels of estradiol and prolactin during pregnancy with undetectable levels of FSH and LH. The blood levels of all these sex hormones returned to normal in the puerperium (Table 2). She did not require specific therapy, because she was asymptomatic all along. Her bone density was normal both before and after pregnancy.

**Statistical Correlations**

In doing the statistical correlations, we included additional sets of data before and after delivery to increase the power of analysis. Regarding the problem of parathyroid hormone (PTH) levels < 1, we analyzed the data considering these values as 1. We found a statistically significant correlation between serum calcitriol and serum estradiol. There was a negative correlation between serum calcitriol and serum PTH, but this did not reach the level of statistical significance. In calculating this correlation, we expressed as 1 pmol/L all values that were reported as < 1 pmol/L. There was no correlation between calcitriol and serum calcium, urine calcium, and calcium/creatinine ratio.

**Discussion**

Sarcoidosis complicating pregnancy was first reported by Nordland et al.\(^\text{13}\) in 1946. Their patient, who had idiopathic thrombocytopenic purpura and sarcoidosis of
the spleen, underwent splenectomy and subsequently had a normal delivery. Mayock et al\(^6\) studied 16 pregnancies in 10 patients with sarcoidosis and found that lymphadenopathy, parenchymal lung lesions, and hyperglobulinemia improved during pregnancy and returned after delivery, while chronic uveitis did not improve. Djrolo et al\(^7\) reported a 29-year-old woman who acquired skin lesions, polyarthritis, and hilar adenopathy after her first delivery; these lesions responded to treatment but relapsed after her second delivery 6 years later.

Hypercalciuria with or without hypercalcemia is a well-known complication of sarcoidosis. Its prevalence varies between 15% and 62%.\(^1\)–\(^4\) The pathogenesis of hypercalciuria in sarcoidosis is not fully understood.\(^4\) Meyrier et al\(^8\), who studied 39 patients with thoracic sarcoidosis, concluded that intestinal calcium hyperabsorption due to high serum levels of calcitriol probably was responsible for hypercalciuria. They proposed that bone resorption due to calcitriol in osteoclasts and/or bone resorption to protect the integrity of maternal skeleton.

Physiologic requirements for calcium increase during normal pregnancy to meet the needs of growing fetus and to maintain maternal plasma and bone calcium concentrations.\(^1\) Gertner et al\(^15\) described pregnancy as a state of physiologic absorptive hypercalciuria. These authors examined the effects of pregnancy on the intestinal absorption and renal excretion of calcium, circulating calcitriol levels, and indexes of PTH function in 16 healthy women during and after pregnancy. They found that calcemic response to oral calcium, urinary calcium excretion, and serum calcitriol were significantly elevated throughout pregnancy. Indexes of PTH were normal or reduced in that study. In a study of interrelations of calcium-regularizing hormones during normal pregnancy, Whitehead et al\(^16\) reported increased concentrations of both calcitriol and calcitonin with low-normal PTH levels. They postulated that the increased calcitriol enables pregnant women to meet the increased physiologic needs for calcium by enhancing intestinal calcium absorption. Simultaneous rise in calcitonin opposes the effects of calcitriol on bone resorption to protect the integrity of maternal skeleton.

Most of the reports\(^5\)–\(^10\) on sarcoidosis and pregnancy have not addressed deranged calcium metabolism in pregnant women. Agha et al\(^17\) reviewed 18 patients with sarcoidosis during 35 pregnancies. Six of their patients had hypercalcemia, which remained unchanged during pregnancy. That study made no mention of hypercalciuria. Deranged calcium metabolism in pregnant women with sarcoidosis has not been extensively studied.

At diagnosis following her first pregnancy, our patient had normocalcemic hypercalciuria, which subsided spontaneously. Hypercalciuria recurred during her second pregnancy, which continued to persist, albeit, at lower levels, until 60 months after her second delivery.

It is well known that extrarenal synthesis of calcitriol, which is not as tightly regulated as in the kidneys, is central to the pathogenesis of abnormal calcium homeostasis in sarcoidosis.\(^4,15\) Once formed, calcitriol regulates calcium homeostasis by increasing GI absorption of calcium and phosphate. In addition, it stimulates osteoclast-mediated bone resorption.\(^4,19\) Elevated calcitriol also has a direct suppressing effect on PTH secretion.\(^4,18,19\)

In our patient, hypercalciuria probably was due to the combined effects of the pregnancy-related increase in urinary calcium excretion and “sarcoidosis activity” \(\text{per se}\), because it was associated with an increase in calcitriol levels. This hypercalciuria did not seem to have any obvious deleterious effect on her bone density.

The literature is split regarding serum PTH levels in normal pregnancy and also in sarcoidosis.\(^1,11,15,16,20,21\) Cushard et al\(^21\) found unmeasurably low levels of PTH in 19 of 20 unselected patients with sarcoidosis and normocalcemia, and postulated that most patients with sarcoidosis are in a state of functional hypoparathyroidism.

### Table 2—Calcium and Hormonal Alterations Before, During Second Pregnancy, and Puerperium

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Normal Range</th>
<th>Before Pregnancy</th>
<th>First Trimester*</th>
<th>Second Trimester*</th>
<th>36th Week</th>
<th>6 mo Postpartum</th>
<th>18 mo Postpartum</th>
<th>60 mo Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h urine calcium, mmol/d</td>
<td>&lt;7.0</td>
<td>6.4</td>
<td>9.55</td>
<td>11.67</td>
<td>10.5</td>
<td>8.8</td>
<td>7.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Serum total calcium, mmol/L</td>
<td>2.2–2.6</td>
<td>2.32</td>
<td>2.14</td>
<td>2.16</td>
<td>2.03</td>
<td>2.43</td>
<td>2.24</td>
<td>2.3</td>
</tr>
<tr>
<td>Serum ionizing calcium, mmol/L</td>
<td>1.2–1.35</td>
<td>1.26</td>
<td>1.295</td>
<td>1.23</td>
<td>1.20</td>
<td>1.29</td>
<td>1.22</td>
<td>1.24</td>
</tr>
<tr>
<td>25 OH vitamin D, nmol/L</td>
<td>36–208</td>
<td>49</td>
<td>47.5</td>
<td>72.3</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,25(OH)(_2) D(_3), pM/L</td>
<td>38–133</td>
<td>96</td>
<td>128.5</td>
<td>164.3</td>
<td>199</td>
<td>58</td>
<td>220</td>
<td>185</td>
</tr>
<tr>
<td>Serum PTH, pM/L</td>
<td>1.3–7.6</td>
<td>1.2</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>4</td>
</tr>
<tr>
<td>Serum ACE, U/L</td>
<td>9–63</td>
<td>54</td>
<td>51.5</td>
<td>52</td>
<td>56</td>
<td>39</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Serum estradiol, pM/L</td>
<td>0–1.468</td>
<td>87</td>
<td>2226</td>
<td>10195.3</td>
<td>23460</td>
<td>44</td>
<td>355</td>
<td>174</td>
</tr>
<tr>
<td>Serum prolactin, µg/L</td>
<td>9–208</td>
<td>7.9</td>
<td>36.3</td>
<td>93.13</td>
<td>138.5</td>
<td>22.8</td>
<td>7.7</td>
<td>7.1</td>
</tr>
<tr>
<td>Serum LH, IU/L</td>
<td>0.1–1.5</td>
<td>4.5</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1.8</td>
<td>3.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Serum FSH, IU/L</td>
<td>1.5–33.4</td>
<td>5.2</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>5</td>
<td>2.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Serum creatinine, µmol/L</td>
<td>7.0–120</td>
<td>75</td>
<td>63.5</td>
<td>57</td>
<td>51</td>
<td>50</td>
<td>77</td>
<td>69</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>38–50</td>
<td>50</td>
<td>49</td>
<td>37.3</td>
<td>35</td>
<td>53</td>
<td>48</td>
<td>43</td>
</tr>
</tbody>
</table>

*Represents mean values of the trimester.


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However, it is difficult to explain why normocalcemic patients should have low PTH level, because there is no apparent signal for PTH suppression. Alberts and Van Den Berg observed 39 patients with sarcoidosis for 1 to 4 years and proposed that an increased sensitivity of target organs to calcitriol may be responsible for hypercalcemia, hypercalcemia, or both. Our patient had undetectable levels of serum PTH throughout pregnancy. Her very low level of PTH might be due to pregnancy and/or suppression of PTH secretion by increased levels of calcitriol.

All the biochemical abnormalities in this patient go well with sarcoidosis and pregnancy-related physiologic alterations in calcium metabolism. In her case, the sources of calcitriol are renal, placental, and probably from the granulomatous tissue. It is known that hormones that are increased during pregnancy, such as prolactin and human placental lactogen, can directly increase production of 1,25 dihydroxycholecalciferol in primary chick kidney cell cultures. Whitehead et al suggested that similar mechanisms might operate in human beings. The suggestion in literature concerning the stimulatory effect of estrogens on the renal 1a-hydroxylase enzyme is supported by the significant positive correlation between serum calcitriol and estradiol levels that we observed. We still need to explain the finding of sustained low iPTH levels with normal ionized calcium levels in blood. We believe that the primary defect in this patient is increased calcitriol produced from sarcoid tissue, placenta, and the kidneys. Her hypoparathyroidism probably is the result of increased calcitriol acting directly on the parathyroid glands and suppressing PTH secretion. Normal serum calcium may be the result of calcitriol-mediated hyperabsorption of calcium from the gut, which would tend to increase serum calcium, in combination with undetectable PTH, which would tend to decrease serum calcium, leading to normocalcemia. However, hypercalcemia may be the result of the combined effect of increased absorption of calcium from the gut, leading to increased filtration of calcium, and decreased renal tubular reabsorption of calcium, as a result of undetectable PTH. It is still not clear what level of calcitriol is needed to produce the hypercalcemia that is observed in some patients.

**Conclusion**

Pregnancy complicating sarcoidosis is a well-documented entity. Physiologic changes in mineral metabolism during pregnancy can complicate sarcoidosis-related calcium disturbances. An increased level of calcitriol is central to the calcium abnormalities in sarcoidosis, which lead to hypercalcemia and undetectable levels of PTH, throughout pregnancy, in the presence of normal serum calcium. This report also highlights the familial occurrence of sarcoidosis.

**References**

2. Gupta SK, Gupta S. Sarcoidosis in India: a review of 125 biopsy-proven cases from Eastern India. Sarcoidosis 1990; 7:43–49