Hyperthyroidism after pregnancy in a patient with rheumatoid arthritis

A case report

P. D. NAIDOO

Summary

A 42-year-old Indian woman with long-standing rheumatoid arthritis became pregnant. Exacerbation of her arthritis during pregnancy and in the puerperium is described and mechanisms for the deterioration in her condition are postulated. Two months after delivery, thyrotoxicosis was suspected because of marked weight loss. Initially the interpretation of her thyroid function was difficult because of certain unusual biochemical findings, the reasons for which are discussed.


In 1938 Hench commented that rheumatoid arthritis in pregnancy 'finds it difficult to progress or indeed to do otherwise than to beat a rather precipitous retreat'. While this statement is true for the majority of patients, in 27% the rheumatoid...
arthritis either remains the same or deteriorates. A pregnant patient may have the classical signs and symptoms of hyperthyroidism such as goitre, excessive sweating and heat intolerance. Although thyroid function tests are altered, the pregnant woman remains euthyroid. Increases in the serum thyroid binding globulins result in elevated total thyroxine (T4) levels. The free thyroxine concentration and the rate of thyroxine production, however, probably remain unchanged during pregnancy.

Peripheral thyroid hormone production may be deranged in acute and chronic illnesses. This may result in abnormal, elevated or depressed serum T4 levels and decreased serum tri-iodothyronine (T3) levels. The exacerbation of the patient's rheumatoid arthritis is the probable explanation for the persistently normal serum total T4 and T3 levels despite the high free thyroxine index.

**Case report**

In 1977 a 38-year-old Indian woman, who had suffered from rheumatoid arthritis since 1973, was referred to the arthritis clinic, King Edward VIII Hospital, for control of her disease. On examination she had signs of active disease; she also had a goitre but was found to be euthyroid both clinically and on biochemical investigations. Parenteral gold administration resulted in marked symptomatic and functional improvement. Two years later gold was stopped when she complained of amenorrhoea for 2 months. The pregnancy test was positive but a spontaneous abortion occurred at 12 weeks' gestation. This was followed by an exacerbation of her arthritis which was controlled with non-steroidal anti-inflammatory drugs (NSAIDs).

In 1981 she became pregnant and came to the clinic complaining of a flare-up of her arthritis. On examination she was estimated to be about 10 weeks' pregnant. The Ritchie index was 35, confirming active disease. In addition there was marked bilateral limitation of the range of movement of her shoulder and hip joints. She obtained some symptomatic relief from prednisone 5 mg daily and ibuprofen 200 mg 3 times daily throughout pregnancy. Intra-articular steroid injections into both shoulder joints resulted in greater mobility. She was then referred to the antenatal clinic. Records of her visits to the clinic show a progressive decrease in weight (Fig. 1), with some lessening of disease activity from the second trimester onwards. At term a normal female infant weighing 2500 g was delivered by caesarean section.

![Fig. 2. Exophthalmos — more marked on the left.](image)

**TABLE I. THYROID FUNCTION TESTS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Treatment</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4 (mmol/l)</td>
<td>11.3</td>
<td>11.9</td>
<td>3.5 - 12.5</td>
<td></td>
</tr>
<tr>
<td>THBC (mmol/l)</td>
<td>79</td>
<td>70</td>
<td>117 - 92</td>
<td></td>
</tr>
<tr>
<td>FT3 (mmol/l)</td>
<td>14.3</td>
<td>17</td>
<td>3.5 - 2.5</td>
<td></td>
</tr>
<tr>
<td>FT4 (mmol/l)</td>
<td>1.5</td>
<td>1.92</td>
<td>0.7 - 2.1</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

This patient demonstrated several interesting and unusual features of the management of rheumatoid arthritis during pregnancy. In a retrospective study Neely and Persellin found that while 63% of the patients showed remission of the symptoms of rheumatoid arthritis during pregnancy 25% failed to improve. Although the factors responsible for improvement are not known, two theories have been put forward. One is that increased cortisol levels in pregnancy may suppress the activity of rheumatoid arthritis. This postulate has not been substantiated by clinical trials. Furthermore it has been shown that some pregnant patients with exacerbation of their rheumatoid arthritis had increased serum cortisol levels while others in remission had normal cortisol levels.

Another explanation is related to the increase in specific plasma proteins during gestation. One of these, an α2-pregnancy-associated globulin (α2-PAG) also called pregnancy zone...
protein, can be demonstrated in the serum of 80% of pregnant women. This protein level which helps to rise by the end of the first trimester falls slowly after delivery until it returns to a lower concentration by the end of the puerperium. This protein has been shown to suppress granulocyte and lymphocyte activity in vitro. A possible explanation for the failure of 25% of pregnant females with rheumatoid arthritis to improve is that these patients do not synthesize sufficient amounts of this α2-PAG during pregnancy, thereby failing to suppress the inflammatory process. This hypothesis may account for the exacerbation of rheumatoid arthritis during the first trimester of pregnancy and in the puerperium in the patient described here. The absence of α2-PAG during the first 9–12 weeks of pregnancy has been found to be associated with a high risk of spontaneous abortion. This may explain the patient's spontaneous abortion in 1979.

Another unusual aspect of this patient's pregnancy was her progressive weight loss which was contrary to the expected weight gain of approximately 0.5 kg weekly (Fig. 1). One possibility is that her pregnancy may have precipitated her hyperthyroid state. This is a difficult diagnosis to make during pregnancy since some of the manifestations such as goitre and heat intolerance are common to both conditions. In addition she had a goitre before pregnancy. As hyperthyroidism was not suspected during pregnancy this assumption remains speculative.

It can be further speculated that the patient developed auto-immune thyroiditis as part of the spectrum of organ-specific diseases. Tests to demonstrate associated organ-specific autoimmune diseases were negative. Also there was no clinical evidence of keratoconjunctivitis sicca, which together with rheumatoid arthritis (Sjögren's syndrome) is known to be associated with auto-immune thyroiditis.

Hyperthyroid patients usually have elevated serum total T₄ and T₃ levels. In fact, a high serum T₃ level has been postulated to be a sensitive index of increased thyroid activity and therefore an invaluable finding in hyperthyroidism. However, in this patient these parameters remained in the upper normal range on repeated testing (Table I).

Acute and chronic systemic illnesses are the major cause of abnormal thyroid function tests. The decreased peripheral deiodination of T₄ to T₃ is thought to be the reason for the normal T₃ level in these patients. This explanation, which was advocated for ill euthyroid patients, could be extrapolated to ill hyperthyroid patients. Serum thyroxine levels may be normal, elevated or depressed in very ill patients. Chopra et al. have suggested that an inhibitor of T₃ binding may be present in the sera of these patients. This inhibitor has characteristics similar to IgM and is thought specifically to inhibit the binding of thyroid hormone to thyroid binding globulin (TBG). Rheumatoid arthritis as a systemic illness could therefore have accounted for the normal serum T₃ level in this patient. The clue to the diagnosis, however, was the low thyroid hormone binding capacity which is indicative of decreased T₃ binding sites on TBG. Hyperthyroidism as a systemic illness could therefore have accounted for the normal serum T₃ level in this patient. The clue to the diagnosis, however, was the low thyroid hormone binding capacity which is indicative of decreased T₃ binding sites on TBG. Coupled with the TRH test and radioactive iodine uptake there was no doubt that this patient was hyperthyroid. It is worth noting that the serum T₄ and T₃ levels reflect bound and free levels. Had free serum T₄ and T₃ levels been measured they would, in all probability, have been elevated.

An additional problem was the use of NSAIDs during pregnancy since they are known to cause premature closure of the ductus arteriosus in animals. However, this patient responded to ibuprofen 200 mg 3 times daily and prednisone 5 mg daily and there were no ill-effects on the baby.

Low doses (20–50 mg) of steroids are thought to impair TSH response to TRH-tests. However, this patient's dose was 'physiological'. Salicylates were withheld throughout gestation because they have been reported to prolong gestation and labour. In addition salicylates inhibit T₃ binding to pre-albumin resulting in a low serum T₃ concentration.

Teratogenicity in animals was the reason for discontinuing gold injections in 1978 when the patient developed amenorrhoea. It is possible that the subsequent spontaneous abortion was related to this therapy since it is uncommon for rheumatoid arthritis to cause abortion.

The effect of rheumatoid arthritis on subsequent fertility is unknown. Kay and Bach suggested lowered fertility in females both before and after the onset of rheumatoid arthritis. This patient admitted that she tried unsuccessfully to become pregnant after her first pregnancy in 1960. The subsequent development in 1973 of rheumatoid arthritis with hip joint involvement might further explain her decreased fertility.

It is possible that the stress of pregnancy after a 20-year wait together with the caesarean section and the exacerbation of her rheumatoid arthritis could have precipitated hyperthyroidism. Another postulated mechanism is that stress may depress the lymphoid system by activation of the corticotropic-releasing factor ACTH-cortisol axis.

There is probably an inherited defect in suppressor T-lymphocyte activity. Stress might further decrease the surveillance capacity of these T-lymphocytes. A particular clone of helper T lymphocytes directed at the thyroid gland may therefore escape suppression and initiate hyperthyroidism.

Graves' disease has long been recognized as having remissions and exacerbations. It has been suggested that 'stress'-induced hyperthyroidism is more prone to remission. However, this patient was also given carbimazole; either the therapy and/or the cessation of stress could have contributed to the induction of remission. Maybe this combination had a synergistic action. She remains euthyroid to this day.

Hughes said: 'One of the attractions of rheumatology is that it remains a highly clinical art.' The sequence of clinical events in this patient fully supports this statement.

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REFERENCES