Maternal age and the risk of developing ankylosing spondylitis

We read with interest the article by Weinreich and colleagues. They showed that transgenic mice born to mothers aged 8 months or older had a significantly lower frequency of murine ankylosing spondylitis (AS) compared to younger mice. They speculated that an age-related increase in maternal antibody levels resulted in increased protection of offspring against a ubiquitous, potentially arthropathic, micro-organism. In humans, as in the mouse model, environmental factors may influence the development of ankylosing spondylitis (AS). We sought evidence that the age of conception in women with AS influences the risk of their offspring developing the disease.

We collected data from 3473 patients with AS, regarding the age, and AS status, of relatives. Of the 146 patients who had AS, 73 had AS, and 73 did not have AS. The data was collected from the Royal National Hospital for Rheumatic Diseases (RNHRD), London, and sixty five were recruited from the Royal National Hospital for Rheumatic Diseases, Bath, BA1 1RL.

TABLE 1

<table>
<thead>
<tr>
<th>Group</th>
<th>AS mother: AS child mean (SD)</th>
<th>AS mother: non AS child mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at childbirth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All mothers</td>
<td>25.56 (4.98)</td>
<td>25.56 (4.98)</td>
</tr>
<tr>
<td>Mothers of daughters</td>
<td>25.67 (3.37)</td>
<td>25.67 (3.37)</td>
</tr>
<tr>
<td>Mothers of sons</td>
<td>25.67 (3.37)</td>
<td>25.67 (3.37)</td>
</tr>
</tbody>
</table>

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LETTER TO THE EDITOR

Methotrexate and triamterene—a potentially fatal combination?

A 57 year old woman had been treated for several years with diclofenac 150 mg/day, atenolol 50 mg/day, and triamterene/hydrochlorothiazide 50/25 mg/day for rheumatoid arthritis (RA) and hypertension. Her doctor started treatment with methotrexate 5 mg/week for active RA. At the start of methotrexate treatment her full blood count was normal except for a haemoglobin of 10.1 g/dl. Renal and liver function were not checked. She weighed 68.5 kg. After one month her haemoglobin had fallen to 8.0 g/dl and her white cell count to 3.6 x 10^9/l and both were markedly reduced. She continued taking methotrexate, but her haemoglobin had fallen to 7.9 g/dl and her white cell count to 2.4 x 10^9/l. She was admitted to hospital where her white cell count was 0.9 x 10^9/l, platelets 1.5 x 10^10/l, serum urea 20.8 mmol/l, and creatinine 148 µmol/l. Urine analysis, liver function tests, and chest x ray were unremarkable. Plasma folate was low at 1.6 µg/l (reference range 1.9—9.0). Cultures of body fluids were subsequently sterile.

She was treated for presumed methotrexate induced bone marrow suppression, with blood products and antimicrobials, discontinuation of usual medication, and, on haematological advice, oral folic acid 10 mg/day. Her white cell count fell over the next 48 hours (2.2 x 10^9/l, neutrophils 1.3 x 10^9/l) and a bone marrow biopsy showed features consistent with partial treated triamterene induced megaloblasticosis. Oral folic acid 15 mg four times daily was substituted for folic acid and five days later her full blood count and renal function had returned to normal (Hb 10.3 g/dl, white cell count 6.1 x 10^9/l, platelets 268 x 10^9/l, serum urea 2.8 mmol/l, and creatinine 90 µmol/l).

Methotrexate is a folate antagonist, competing with folic acid for active transport into cells and competitively inhibiting dihydrofolate reductase (DHFR). The risk of marrow toxicity may be increased by co-prescribing other folate antagonists.

Triamterene is a potassium sparing diuretic, structurally similar to folate, with anti-folate activity. It inhibits DHFR in vivo and in vitro and inhibits folate acid absorption in the rat.

Patients treated with high doses of triamterene for ascertes may develop megaloblastic anaemia, which responds to folinic acid treatment. Thus, there are good theoretical reasons for this patient developing marrow toxicity as a result of an interaction between methotrexate and triamterene. Long term triamterene treatment may have rendered her folate deficient, the two drugs may have had a synergistic effect on DHFR, or both of these mechanisms may have been involved.

The lack of information on pre-treatment renal function means that the possibility that toxicity developed as a result of reduced renal clearance of methotrexate cannot be excluded. Hypertension or the combination of medication may have resulted in compromised renal function. However, the fact that the serum urea was increased out of proportion to the creatinine rise suggests that her abnormal renal function may have been secondary to dehydration consequent upon her illness, rather than the cause of it.

In addition to this suspected drug interaction, this case highlights several other important points about the prescribing of methotrexate. It should be given under specialist supervision, using inferior monitoring of full blood count, renal and liver function. The patient and doctor should be warned about possible side effects and advised to stop the drug should suspected side effects develop. Extra caution is required in patients with renal impairment or receiving nephrotoxic drugs.

Finally folic acid has no place in the management of methotrexate induced paroxysmal nocturnal haemoglobinuria, the reduced form of folate, folic acid, should be given as soon as the condition is suspected.
Methotrexate and triamterene—a potentially fatal combination?

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Ann Rheum Dis 1997 56: 209
doi: 10.1136/ard.56.3.209a

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