MATTERS ARISING

Maternal age and the risk of developing ankylosing spondylitis

We read with interest the article by Weinreich and colleagues.¹ They showed that transgenic mice born to mothers aged 8 months or older had a significantly lower frequency of murine ankylosing enthesopathy than mice born to younger mothers. They speculated that an age related increase in maternal antibody levels resulted in increasing protection of offspring against a ubiquitous, potentially arthritogenic, micro-organism. In humans, as in the mouse model, environmental factors must influence the development of ankylosing spondylitis (AS). We sought evidence that the age of conception in women with AS influenced the risk of their offspring developing disease.

We collected data from 3473 patients with AS, regarding the age, and AS status, of relatives. Nine hundred and sixty two were female, male: female ratio 2.6:1. Six hundred and sixty five were recruited from the Royal National Hospital for Rheumatic Diseases (RNHRD), 2779 from the National Ankylosing Spondylitis Society (NASS), and 29 were relatives of RNHRD patients or NASS members, but were not RNHRD patients or NASS members themselves. Those from the RNHRD have been confirmed, by a rheumatologist, as having AS according to the New York criteria.² The diagnosis of AS in the overall patient population has been validated in three separate cohorts in which 100% of 146 patients had AS (personal communications M Brown, Oxford), 92.7% of 330 patients had AS (personal communications K Gomez, Bath), and 96% of 50 patients had AS.³ Data were available for 39 pairs in which both mother and offspring had AS (21 mother:daughter pairs, 18 mother:son pairs). There were no families with data available for more than one mother:child pair. The higher than expected ratio of mother:daughter to mother:son pairs is the subject of an ongoing investigation. From our data base we chose 39 control pairs, where the mother had AS and the offspring did not, by matching the offspring for sex and age to the nearest year. We were able to match the offspring for birth rank in 37 cases (20 mother:daughter pairs, 17 mother:son pairs). The offspring were not matched for sibship size. The maternal ages at birth of offspring are shown (see table 1). Using paired *t* tests, we compared maternal ages at childbirth in the groups where the offspring had AS, and where the offspring did not have AS. The difference in the maternal age at childbirth was significant only when comparing mothers of sons with AS and

mothers of sons without AS ($p = 0.04$; difference in mean maternal age at childbirth = 2.78 years). Mothers with AS, whose sons had AS, had given birth at a older age than those whose sons did not have AS.

Unlike the situation in the murine model, we find no evidence that increasing maternal age in humans is protective against the development of AS. However, the number of pairs available for our analysis was small. The influence of age at conception, on the development of AS in the offspring, remains an interesting area that deserves further attention.

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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 $3.6 \times 10^9/l$ and she developed mouth ulcers, dyspnoea, and easy bruising. She continued taking methotrexate, but after a month of these symptoms was admitted to hospital as an emergency.

On examination she was pale, tachypnoeic, and dehydrated with extensive mucosal ulceration. Investigations showed a pancytopenia with renal impairment (Hb 4.1 g/dl, mean cell volume 89.5 fl, white cell count $3.1 \times 10^9/l$, neutrophils $2.0 \times 10^9/l$, lymphocytes $0.5 \times 10^9/l$, platelets $31 \times 10^9/l$, serum urea

20.8 mmol/l, and creatinine 148 $\mu\text{mol/l}$). Urine analysis, liver function tests, and chest x ray were unremarkable. Plasma folate was low at 1.6 $\mu\text{g/l}$ (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 ($2.2 \times 10^9/l$, neutrophils $1.3 \times 10^9/l$), and a bone marrow biopsy showed features consistent with partially treated methotrexate induced megaloblastosis. 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 10.5 g/dl, white cell count $6.1 \times 10^9/l$, platelets $268 \times 10^9/l$, serum urea 2.8 mmol/l, and creatinine 90 $\mu\text{mol/l}$).

Methotrexate is a folate antagonist, competing with folate 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.¹

Triamterene is a potassium sparing diuretic, structurally similar to folate, with anti-folate activity. It inhibits DHFR *in vivo*² and *in vitro*³ and inhibits folic acid absorption in the rat.⁴ Patients treated with high doses of triamterene for ascites may develop megaloblastic anaemia, which responds to folic acid treatment.³⁻⁵ 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, and both parameters returned to normal with rehydration 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 with baseline and regular monitoring of full blood count, renal and liver function.⁶ 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 impairment⁷ or receiving nephrotoxic drugs.¹ Finally folic acid has no place in the management of methotrexate induced pancytopenia, the reduced form of folate, folic acid, should be given as soon as the condition is suspected.⁸

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Table 1 Age of mothers with AS at birth of children, with AS and without AS

	AS mother: AS child mean (SD) maternal age at child birth	AS mother: non AS child mean (SD) maternal age at child birth
All mothers (n=39)	26.79 (4.14)	25.56 (4.98)
Mothers of daughters (n=21)	25.67 (3.37)	27.62 (5.17)
Mothers of sons (n=18)	28.11 (4.64)	25.33 (4.59)

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