REVIEW

Multiple sclerosis and pregnancy

A R Lorenzi, H L Ford

Postgrad Med J 2002;**78**:460–464

Multiple sclerosis causes disability in young adults and, like most autoimmune diseases, affects women more commonly than men. The disease can therefore present at a time when many have, or are considering, starting a family. The effect of pregnancy on the outcome of multiple sclerosis is reviewed and the management of pregnant women who have multiple sclerosis is discussed.

Multiple sclerosis, an inflammatory demyelinating disease of the central nervous system, is the commonest cause of neurological disability in young adults in the UK. Fifty per cent of multiple sclerosis patients will require the aid of a stick to walk 15 years after the diagnosis.[1] Prevalence rates in the England vary between 80 and 287 per 100 000 with higher rates in northern Scotland and Orkney.[2] Typically, females are affected nearly twice as commonly as males.

In women multiple sclerosis very frequently manifests at a time when many will be considering pregnancy, and bringing up children can be expected to occur at a time of increasing disability. Despite this, little is known about the effect of pregnancy on disease progression or of the disease process on the outcome of pregnancy. There have been few good trials of adequate duration and as such we are poorly equipped to discuss these issues with patients considering pregnancy. Many studies are retrospective and therefore are limited by recall bias.

We review the available information about relapse rates during pregnancy and the puerperium, anaesthetic and radiological considerations, treatment options, and finally discuss the immunological changes occurring during pregnancy and what we can learn from these observations about the pathogenesis of multiple sclerosis.

Box 1: Key points

- Multiple sclerosis is the commonest cause of disability in young adults in the UK.
- Women are affected twice as commonly as men and this often coincides with bringing up a family.
- Pregnancy is not likely to adversely affect disease progression in women with multiple sclerosis.
- There is weak evidence to suggest that pregnancy may improve the course of multiple sclerosis or delay its onset.
- Steroids are not contraindicated in pregnancy but they should be used with caution after discussion about the risks and benefits.
- Planning adequate postnatal support for a family should take into account the increased risk of relapse postpartum.

See end of article for authors' affiliations

Correspondence to: Dr A R Lorenzi, Molecular Medicine Unit, Clinical Sciences Building, St James's University Hospital, Leeds LS9 7TF, UK; medarl@south-01.novell.leeds.ac.uk

Submitted 30 April 2002
Accepted 15 May 2002

MULTIPLE SCLEROSIS AND PREGNANCY—IS THERE AN ADVERSE RELATIONSHIP?

Onset of multiple sclerosis during pregnancy and disease relationship to parity

The nine months of pregnancy are generally associated with a reduction in the number of relapses in multiple sclerosis (see below). The onset of multiple sclerosis should also theoretically be reduced during times of pregnancy. In a retrospective study Poser and Poser found the onset and deterioration of multiple sclerosis occurring during the nine months of pregnancy was half that seen in the six months immediately postpartum, despite the different periods of time.[3] In a population based study, Runmarker and Anderson estimated the risk of onset of multiple sclerosis during pregnancy when compared with non-pregnancy periods, by comparing data from their multiple sclerosis cohort with Swedish national census data.[4] Their cohort contained 153 female patients (age 15–50) with multiple sclerosis of whom 100 were used in the analysis. They reported no patients with onset of multiple sclerosis in the nine months of pregnancy but nine patients developed multiple sclerosis in the eight calendar months after delivery. The risk of onset was significantly lower in the eight months preceding the delivery compared with the eight months after it, although the risk at this time was no greater than at other non-pregnancy periods. They also identified an increased risk of multiple sclerosis in nulliparous women compared with parous women that appears not to be associated with a reduced fecundity in patients who have, or go on to develop, multiple sclerosis. Of 153 patients with clinically definite or probable multiple sclerosis, 74 were nulliparous at onset compared with an age matched expected rate of 50.9. The risk ratio increased with age.

Relapse rate during the time of pregnancy and the puerperium

The majority of studies, retrospective and prospective, looking at relapse rate during and immediately after pregnancy have concluded that there is a reduced frequency of relapse during

Abbreviations: EDSS, expanded disability status scale; HLA, human leucocyte antigen; IL, interleukin; MRI, magnetic resonance imaging; NK, natural killer

pregnancy followed by an increase in relapse rate in the puerperium.[3 5 6] Others have found no reduction in the relapse rate during pregnancy compared with baseline, while confirming the increased relapse rate in the puerperium.[7] The PRIMS study group recently reported a prospective study of 254 patients with multiple sclerosis followed up during pregnancy and for 12 months postpartum. All the women enrolled had previously been diagnosed with multiple sclerosis, according to the Poser classification,[8] and all had been pregnant for at least four weeks, but less than 36 weeks, before enrolment. Recruitment was at the discretion of the woman's neurologist and all European neurologists were invited to recruit patients. Nearly the whole cohort (n = 246) had a relapsing-remitting disease course. They found a reduction in relapse rate during pregnancy (using prepregnancy relapse rate as a control) which was most pronounced in the last trimester.[9] This was followed by an almost equivalent increase in relapse rate in the three months immediately postpartum, before returning to prepregnancy rates. Of note, however, was that 16 women received corticosteroids during pregnancy and 40 women received some form of immunosuppression in the first six months postpartum. Thus, it is possible that they may have underestimated the true relapse rate. In a prospective study, Dezza Sadovnick *et al* compared 42 pregnant multiple sclerosis patients with "matched" and "self" controls. Matched patients were patients of the same age with identical disease onset and pattern, and self control data were taken from data collected as part of their cohort analysis in the preceding year. They found a reduction in relapse rate during the last trimester of pregnancy in patients compared with aged matched controls but not when compared with self relapse rates before the onset of pregnancy (although a trend toward reduction in the third trimester was noted, this did not achieve statistical significance).[10]

Impact of pregnancy on disease progression

Although the majority of recent studies point to an increase in relapse rate in the puerperium, when the period of pregnancy and puerperium is considered as a whole, there is no overall change in the total number of relapses seen. This is consistent with many of the early studies from the 1950s and 1960s where the two periods were not separated in analysis and where no effect of pregnancy on relapse rate was reported.[11–13] Data from most studies suggest no adverse impact of pregnancy on disease progression, although few have followed patients up for a sufficient length of time. In reported studies no association between pregnancy and long term disability has been found, although 10 years is the longest follow up reported.[3 7 14 15]

There is some evidence to suggest that pregnancy may slow the rate of progression to predefined endpoint measures, such as walking with a stick or the onset of secondary progressive multiple sclerosis.[16] The course of disease in parous women may be improved when compared with nulliparous women, although age of onset of multiple sclerosis and/or an effect on conceptive behaviour in more severely disabled women may be confounding.[4] Verdu *et al* found that time to wheelchair use was increased by 50% where women developed multiple sclerosis before pregnancy when compared with the group who had no pregnancies after their diagnosis.[17]

Radiological imaging

Magnetic resonance imaging (MRI) is increasingly important in the diagnosis and prognosis of multiple sclerosis. Recent trial reports have supported the use of MRI as a prognostic tool in patients presenting with their first episode of symptoms suggestive of demyelination.[18 19] Eighty five per cent of patients with asymptomatic lesions, consistent with demyelination, went on to develop clinically definite multiple sclerosis. This compared with only 11% in those who had a normal scan.[18] The initial lesion load also correlated with disability at 10 years. Seventy five per cent of those with more than 10 lesions at presentation had an expanded disability status scale (EDSS) of >3 at 10 years.[18] Volume of lesion load has also been correlated with EDSS at 10 years. All patients with a total lesion volume of >3 cm^3 at presentation had multiple sclerosis at 10 years and 45% of these had an EDSS >6.[19] It is therefore interesting to note the findings of van Walderveen *et al* who report the MRI appearances of two patients who became pregnant during the course of another longitudinal study tracing MRI appearances in multiple sclerosis.[20] They demonstrated a dramatic reduction in the number of active lesions seen in their patients over the period of their pregnancy. In their first patient, the lesion load fell to zero in the second trimester and in both patients during the third trimester the lesion load was zero. Postpartum these lesions returned. Importantly, however, the changes seen were not associated with a change in the clinical status of the patients, in accordance with previous magnetic resonance studies.[21 22]

It should be noted that there are no data about the safety or otherwise of MRI in pregnancy, although there are no reports of associated fetal abnormality. As with all investigations and treatments in pregnancy, scans should be requested when the outcome may change clinical management.

MANAGEMENT AND TREATMENT DECISIONS

Many women with multiple sclerosis may approach their general practitioner, neurologist, or obstetrician for advice before considering pregnancy. Issues of concern may include risk of relapse and progression as discussed above, analgesia during delivery, interventions to reduce the chance of relapse in the peripartum period and the potential effect, if any, on their child.

Anaesthesia at delivery

Two studies of spinal anaesthesia have reported an association with increased relapse rate postpartum.[23 24] A retrospective case note study suggested an association between the type of anaesthetic given and relapse rate. An increased rate of relapse was found in patients given concentrations of bupivacaine greater than 0.25%, although no difference was reported between patients having local versus epidural blockade.[25]

However, the relapse rate (33%) reported by Bamford *et al* was of the same order as that seen overall in patients postpartum and as such it is difficult to speculate about causality.[24] The PRIMS group found no association between epidural anaesthesia and relapse rate.[9] There appears to be little conclusive evidence to support a role for anaesthesia precipitating exacerbations of multiple sclerosis postpartum. However, this has not been fully evaluated and there is a paucity of recent, primary outcome data in this area. Advances in anaesthetic techniques and agents have been rapid. Further evidence is needed to allow a fully informed discussion about pain relief during delivery for patients with multiple sclerosis.

Outcome of the children born to mothers with multiple sclerosis

A three year prospective study from the Middlesex Hospital reported a normal distribution of weight and head circumference in babies born to mothers with multiple sclerosis.[26] There is no reported evidence to suggest that the children of women with multiple sclerosis are in anyway physically or mentally disadvantaged. The increased frequency of relapse seen in the puerperium may, however, impact on the important early relationship between mother and child. A mother with multiple sclerosis may be temporarily less able to care for her new child if she has a significant relapse. Fatigue is well recognised as a feature of multiple sclerosis[27] and may be more likely to be

a problem postpartum than at other times. These potential problems should be discussed and incorporated into plans for maternity leave and support after the birth. Given the increasing use of immunosuppressive agents appropriate advice on contraception is essential.

Breast feeding and multiple sclerosis

Nelson *et al* retrospectively studied two groups of patients with multiple sclerosis, identified from patients recruited to trials of immunosuppressive agents and patients from a multiple sclerosis centre in Denver.[28] Of these, 483 women were asked retrospectively about time of onset of defining symptoms, frequency of relapse, and breast feeding. They found that relapse rate in the puerperium was independent of breast feeding status. Fifty per cent of patients with multiple sclerosis breast fed their children for an average of 6.3 months. Relapse rate in the breast feeding group was 37.5% compared with 30.5 % (not significant). Breast feeding did not delay the mean time to relapse (3.0 *v* 3.1 months); 69% of relapses in the breast feeding group occurred before the cessation of breast feeding. These findings have subsequently been corroborated.[9]

Interventions to reduce or prevent relapse in the perinatal period

It has been suggested that intravenous immunoglobulin in the postpartum period may potentially reduce the incidence of postpartum relapse.[29 30] To date this has only been studied in an open label observational study from Israel.[31] In nine women with relapsing remitting multiple sclerosis, who in previous pregnancies had had severe or multiple relapses postpartum, intravenous immunoglobulin was administered at a dose of 0.4 g/kg on five of seven days immediately postpartum. Further doses were given in weeks 6 and 12. At six months none had relapsed. No adverse events where reported. A European trial is in preparation.[30]

Remarkably, there is little information regarding the safety of intravenous corticosteroids in pregnancy. The Food and Drug Administration, in their pregnancy categories, list cortisone in category D (positive evidence of human of human fetal risk from marketing or investigational experience, drugs to be used only where there is no safer alternative and where the benefit outweighs the known risk) and prednisone in category B (animal studies have failed to demonstrate a risk to the fetus and there are no adequate trials in pregnant women. The difference is felt to reflect the limited use of cortisone in pregnancy and the subsequent bias in adverse event reporting). There are no controlled trials of high dose corticosteroids in the treatment of multiple sclerosis relapses during pregnancy. Animal studies have demonstrated reduction in fetal growth and compromised central nervous system development with large doses of prenatal corticosteroid. In women with other steroid dependent diseases, fetal adrenal suppression, and hypoglycaemia (usually short term) cleft lip, prematurity and stillbirth have been reported, although again there are limited data in pregnancy.[16 32]

However, in other diseases requiring steroid treatment—asthma, systemic lupus erythematosus, and Crohn's disease for example—active maternal disease may be potentially life threatening both for the mother and fetus. In multiple sclerosis, where there is no evidence for long term benefit with the use of high dose corticosteroid in treating relapse, the decision to treat maybe harder to justify (for current Committee on Safety of Medicines advice see also Stenius-Aarniala *et al*[32]).

In the PRIMS study 40 of 254 women enrolled were treated with a variety of immunosuppressive agents (35 corticosteroid, four azathioprine, and one mitoxantrone) in the first six months postpartum. In the next six months, 27 received corticosteroid, three azathioprine, and six interferon beta-1b. The effect of this treatment on relapse rate is not reported.[9] Azathioprine is not contraindicated in pregnancy, but should not be started[33]; interferon is not licensed in pregnancy.[33]

Can we explain the change in relapse rate during pregnancy and the puerperium?

Pregnancy provides an immunological challenge. The fetus is allogenic, carrying paternally derived antigen. Despite this, the mother carries the fetus till term in normal circumstances. The placenta or "fetoplacental unit" is important and many properties of this interface are known to be actively involved in maintaining a successful pregnancy.

The syncitotrophoblastic layer, in contact with maternal tissue, expresses a minimally polymorphic human leucocyte antigen (HLA) class I molecule, HLA G rather than classical major histocompatibility class proteins.[34] HLA G has been shown to bind and inactivate cytotoxic natural killer (NK) cells. There is also an altered equilibrium between the arms of the CD4+, helper T cell population T_H1 and T_H2. During pregnancy, a shift favouring a T_H2 weighted response is triggered by the secretion of appropriate cytokines from the fetoplacental unit.[35] In experimental animal models, a T_H1 (proinflammatory, cytoxic) profile of cytokines, interleukin (IL)-2, interferon gamma, and tumour necrosis factor retard fetal growth and induce abortion. This cytokine profile promotes responses activating NK cells and macrophages. Differentiation of CD4+ cells into a T_H1 phenotype is inhibited by IL-4 and IL-10. The fetoplacental unit secretes these and other cytokines and hormones with anti-inflammatory properties. IL-4, IL-5, IL-6, IL-10, and progesterone switch maternal immune status to favour a predominantly T_H2 (helper, humoral) profile[36] and IL-10 may increase HLA G expression.[34]

While this may be vital for survival of the fetus, it could also explain why we see an improvement in many autoimmune, inflammatory conditions during pregnancy. For example in one study, 70% of women with rheumatoid arthritis had an improvement in their symptoms during pregnancy.[37] Like rheumatoid arthritis, multiple sclerosis is thought to be a predominantly T cell driven process. In switching to a T_H2 biased state, T cell mediated cytotoxicity is reduced, and it is possible, in multiple sclerosis, that remyelination may be promoted.[38] At term this equilibrium may revert, triggering renewed cytotoxic damage, to myelin in the case of multiple sclerosis, prompting the increase in relapse rate seen.

Current evidence of increased disease activity in the postpartum period identifies a subgroup of patients with multiple sclerosis who may benefit from disease modifying treatment. Further work in this area may lead to a better understanding of the pathology of multiple sclerosis, and potentially many other autoimmune diseases, leading to the development of novel therapeutic strategies.

SUMMARY

Pregnancy does not appear to be associated with an adverse outcome in multiple sclerosis, and may even have a beneficial effect, although follow up data of sufficient length are limited and often not readily applicable in the clinic setting. There is a consensus supporting the observation that the nine months of pregnancy are associated with a reduction in the frequency of relapse, which is followed by an increase in the relapse rate in the six months postpartum. Advances in imaging and the understanding of the immunology of multiple sclerosis and pregnancy may lead to novel theraputic strategies in the future. Currently available evidence for the use of immunosuppressive agents in pregnancy is limited. The use of analgesia during delivery for patients with multiple sclerosis has not been extensively evaluated but there is

Box 2: Key references

- Confavreux C, Hutchinson M, Hours M, *et al*. Rate of pregnancy related relapses in multiple sclerosis. *N Engl J Med* 1998;**339**:285–91.
- Damek DM, Shuster EA. Pregnancy and multiple sclerosis. *Mayo Clin Proc* 1997;**72**:977–89.
- Dezza Sadovnick A, Eisen K, Hashimoto SA, *et al*. Pregnancy and multiple sclerosis. *Arch Neurol* 1994;**51**:1120–4.
- Runmarker B, Anderson O. Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. *Brain* 1995;**118**:253–61.
- Ruollet E, Verdier-Taillefer M-H, Amarenco P, *et al*. Pregancy and multiple sclerosis: a longitudinal study of 125 remittent patients. *J Neurol Neurosurg Psychiatry* 1993;**56**:1062–5.

Questions (answers at end of paper)

(1) True or false: The risk of relapse during the nine months of pregnancy is the same as for the subsequent nine months.

(2) The use of steroids in pregnancy has been associated with which of the following in neonates?
(i) Type I diabetes mellitus
(ii) Type II diabetes mellitus
(iii) Neonatal hypoglycaemia
(iv) Adrenal suppression
(v) Growth retardation

(3) True or false: Multiple sclerosis never presents during pregnancy?

(4) True or false: MRI is a gold standard for the diagnosis of multiple sclerosis?

(5) True or false: Since maternal immunoglobulin crosses the placenta, babies born to mothers with multiple sclerosis have an increased chance of developing the disease.

no substantial evidence to suggest an increased risk of relapse. Chance MRI observations in patients with multiple sclerosis during pregnancy have contributed to our understanding of the impact of pregnancy on the natural history of the disease.

Women should be aware of the risks of relapse during pregnancy and in the postpartum period when planning a pregnancy. Appropriate support should be planned in advance, particularly for the postpartum period. There is no evidence to support previously held beliefs that women with multiple sclerosis should not become pregnant.

ACKNOWLEDGEMENT

The authors are grateful to Professor J J Walker, Professor of Obstetrics and Gynaecology, St James's University Teaching Hospitals, for his review of the manuscript and helpful comments.

Authors' affiliations
A R Lorenzi, H L Ford, Department of Neurology, St James's University Hospital, Leeds, UK

REFERENCES

1 **Weinshenker BG**, Bass B, Rice GP, *et al*. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 1989;**112**:133–46.
2 **Compston A**. Distribution of MS. *McAlpine's multiple sclerosis*. 3rd Ed. Edinburgh: Churchill Livingstone, 1999.
3 **Poser S**, Poser W. Multiple sclerosis and gestation. *Neurology* 1983;**33**:1422–7.
4 **Runmarker B**, Anderson O. Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. *Brain* 1995;**118**:253–61.
5 **Frith JA**, Mcleod JG. Pregnancy and multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1988;**51**:495–8.
6 **Birk K**, Ford C, Smeltzer S, *et al*. The clinical course of multiple sclerosis during pregnancy and the puerperium. *Arch Neurol* 1990;**47**:738–42.
7 **Ruollet E**, Verdier-Taillefer M-H, Amarenco P, *et al*. Pregancy and multiple sclerosis: a longitudinal study of 125 remittent patients. *J Neurol Neurosurg Psychiatry* 1993;**56**:1062–5.
8 **Poser CM**, Paty DW, Scheiner L, *et al*. New diagnostic criteria for multiple sclerosis; guidelines for research protocols. *Ann Neurol* 1983;**13**:227–31.
9 **Confavreux C**, Hutchinson M, Hours M, *et al*. Rate of pregnancy related relapses in multiple sclerosis. *N Engl J Med* 1998;**339**:285–91.
10 **Dezza Sadovnick A**, Eisen K, Hashimoto SA, *et al*. Pregnancy and multiple sclerosis. *Arch Neurol* 1994;**51**:1120–4.
11 **Tillman AJB**. The effect of pregnancy on multiple sclerosis and its management. *Res Publ Assoc Res Nerv Ment Dis* 1950;**28**:548–82.
12 **McAlpine D**, Compston N. Some aspects of the natural history of disseminated sclerosis. *Q J Med* 1952;**21**:135–67.
13 **Ghezzi A**, Caputo D. Pregnancy: a factor influencing the course of multiple sclerosis? *Eur Neurol* 1981;**20**:115–7.
14 **Weinshenker BG**, Rice GPA, Noseworthy JH, *et al*. The natural history of multiple sclerosis: a geographically based study. 3. Multivariate analysis of predictive factors and models of outcome. *Brain* 1991;**114**:1045–56.
15 **Weinshenker BG**, Hader W, Carriere W, *et al*. The influence of pregnancy on disability from multiple sclerosis: a population based study in Middlesex County, Ontario. *Neurology* 1989;**39**:1438–40.
16 **Damek DM**, Shuster EA. Pregnancy and multiple sclerosis. *Mayo Clin Proc* 1997;**72**:977–89.
17 **Verdu P**, Theys P, D'Hooghe MB, *et al*. Pregnancy and multiple sclerosis: the influence on long term disability. *Clin Neurol Neuosurg* 1994;**96**:38–41.
18 **O'Riordan JI**, Thompson AJ, Kingsley DPE, *et al*. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. *Brain* 1998;**121**:495–503.
19 **Sailer M**, O'Riordan JI, Thompson AJ, *et al*. Quantitative MRI in patients with clinically isolated syndromes suggestive of demyelination. *Neurology* 1999;**52**:599–606.
20 **van Walderveen MA**, Tas MW, Barkhof F, *et al*. Magnetic resonance evaluation of disease activity during pregnancy in multiple sclerosis. *Neurology* 1994;**44**:327–9
21 **Koopman RA**, Li DKB, Oger JJF, *et al*. Chronic progressive multiple sclerosis: serial magnetic resonance brain imaging over six months. *Ann Neurol* 1989;**26**:248–56.
22 **Willoughby EW**, Grochowski E, Li DKB, *et al*. Serial magnetic resonance scanning in multiple sclerosis: a second prospective study in relapsing patients. *Ann Neurol* 1989;**25**:43–9.
23 **Stenuit J**, Marchand P. Les sequelles de rachi-anaesthesie. *Acta Neurol Belg* 1968;**68**:626–35.
24 **Bamford C**, Sibley W, Laguna J. Anaesthesia in multiple sclerosis. *Can J Neurol Sci* 1978;**5**:41–4.
25 **Bader AM**, Hunt CO, Datta S, *et al*. Anaesthesia for the obstetric patient with multiple sclerosis. *J Clin Anesth* 1988;**1**:21–4.
26 **Worthington J**, Jones R Crawford M, *et al*. Pregnancy and multiple sclerosis—a three year prospective study. *J Neurol* 1994;**241**: 228–33.
27 **Ford H**, Trigwell P, Johnson M. The nature of fatigue in patients with multiple sclerosis. *J Psychosom Res* 1998;**45**(1 Spec No):33–8.
28 **Nelson L**, Franklin GM, Jones MC and the Multiple Sclerosis Study Group. Risk of multiple sclerosis exacerbation during pregnancy and breast-feeding. *JAMA* 1988;**259**:3441–3.
29 **Achiron A**, Rotstein A, Noy S, *et al*. Intravenous immunoglobulin treatment in the prevention of childbirth-associated acute exacerbations in multiple sclerosis: a pilot study. *J Neurol* 1996;**243**:25–8.
30 **Haas J**. High dose IVIG in the postpartum period for prevention of exacerbations in MS. *Multiple Sclerosis* 2000;**6**(suppl 2):S18–20.
31 **Orvieto R**, Achiron A, Rotstein A, *et al*. Pregnancy and multiple sclerosis: a 2-year experience. *Eur J Obstet Gynecol Reprod Biol* 1999;**82**:191–4.
32 **Stenius-Aarniala B**, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. *Thorax* 1988;**43**:12.
33 **British Medical Association and the Royal Pharmaceutical Society of Great Britain**. *British national formulary*. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2001;**41**.
34 **Thellin O**, Coumans B, Zori W, *et al*. Tolerance to the feto-placental "graft": ten ways to support a child for nine months. *Curr Opin Immunol* 2000;**12**:731–7.
35 **Wegmann TG**, Hui Lin, Guilbert L, *et al*. Bi-directional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a phenomenon? *Immunol Today* 1993;**14**:353–6.
36 **Piccinni M-P**, Scaletti C, Maggi E. Role of hormone controlled Th1 and Th2-type cytokines in successful pregnancy. *J Neuroimmunol* 2000;**109**:30–3.
37 **Da Silva JA**, Spector TD. The role of pregnancy in the course and aetiology of rheumatoid arthritis. *Clin Rheumatol* 1992;**11**:189–94.
38 **Noseworthy J**, Luccinetti C, Rodriguez M, *et al*. Multiple sclerosis. *N Engl J Med* 2000;**343**:938–52.
39 **Jacobs LD**, Beck RW, Simon JH, *et al*. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med* 2000;**343**:938–52.

ANSWERS

(1) False. The risk of relapse in the nine months of pregnancy is reduced when compared with the nine months immediately postpartum. The number of relapses experienced by women over all, however, is unchanged, the benefit gained in the prenatal period being lost in the postpartum period when relapse rate is increased.

(2) True (iii) (iv). There are no randomised clinical trials looking at the outcome of children born to mothers who have had steroids during their pregnancy. The use of steroids is NOT contraindicated during pregnancy and they are often used in low dose to prevent exacerbation of maternal disease.

Adrenal suppression and hypoglycaemia have been reported and should be checked for in neonates. Both are generally reversible. Growth retardation has been reported in some animal models.

(3) False. Population studies show much reduced rates of the onset of multiple sclerosis during pregnancy, together with a lower relapse rate during pregnancy. While it is unusual therefore to see multiple sclerosis present during pregnancy it can occur. Extra caution to rule out other disease mimicking multiple sclerosis should be made, and in particular cerebral vasculitis, thromboembolic stroke, and antiphospholipid syndrome should be considered.

(4) False. MRI alone cannot be used to diagnose multiple sclerosis, but there are increasingly specific MRI criteria to support the diagnosis. One randomised, double blind clinical trial has been reported where a *first episode* of a typical multiple sclerosis symptom and predefined MRI lesion load were used as criteria to start treatment with interferon β1-a.[39]

(5) False. While IgG certainly crosses the placenta, patients with multiple sclerosis rarely have measured pathological immunoglobin in their serum, since immunoglobulin synthesis in multiple sclerosis is primarily intrathecal (forming the basis of the oligoclonal band test performed on cerebrospinal fluid). While this is a simplistic answer, and there may be demyelinating antibodies in the serum of those with multiple sclerosis (for comprehensive review see Noseworthy *et al*[38]), there is no evidence that babies born to mothers with multiple sclerosis have neuronal damage as a consequence of maternal autoantibodies. (Unlike in Graves' disease and systemic lupus erythematosus with anti-Ro antibodies which can mediate neonatal hyperthyroidism and congenital heart block respectively.)

However, there is an undoubted genetically mediated increased susceptibility to developing multiple sclerosis. Concordance rates between monozygotic twins is six times that of dizygotic twins (31% *v* 5%). The absolute risk of multiple sclerosis is less than 5% in a first degree relative but this is 20–40 times the risk in the general population.[38] HLA DR2 confers a significant increase in risk (although protects from type I diabetes mellitus).