Multiple sclerosis and pregnancy

A R Lorenzi, H L Ford

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.

**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.

**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.

**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

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**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.\textsuperscript{9, 10} Others have found no reduction in the relapse rate during pregnancy compared with baseline, while confirming the increased relapse rate in the puerperium.\textsuperscript{9} 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,\textsuperscript{2} and all had been pregnant for at least four weeks, but less than 36 weeks, before enrollment. 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.\textsuperscript{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 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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{14–16}

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.\textsuperscript{17} 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 conceptional behaviour in more severely disabled women may be confounding.\textsuperscript{18} 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.\textsuperscript{19}

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.\textsuperscript{20–22} 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.\textsuperscript{23} 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.\textsuperscript{24} Volume of lesion load has also been correlated with EDSS at 10 years. All patients with a total lesion volume of >3 cm

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 puerperium 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.\textsuperscript{25, 26} 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.\textsuperscript{27}

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.\textsuperscript{28} The PRIMS group found no association between epidural anaesthesia and relapse rate.\textsuperscript{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.\textsuperscript{29} 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\textsuperscript{30} and may be more likely to be
received corticosteroid, three azathioprine, and six interferon beta-1b. The effect of this treatment on relapse rate is not reported. Azathioprine is not contraindicated in pregnancy, but should not be started; interferon is not licensed in pregnancy.

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 syncytiotrophoblastic 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. 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 TH1 and TH2. During pregnancy, a shift favouring a TH2 weighted response is triggered by the secretion of appropriate cytokines from the fetoplacental unit. In experimental animal models, a TH1 (proinflammatory, cytotoxic) 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 TH1 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 TH2 (helper, humoral) profile and IL-10 may increase HLA G expression.

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. Like rheumatoid arthritis, multiple sclerosis is thought to be a predominantly T cell driven process. In switching to a TH2 biased state, T cell mediated cytotoxicity is reduced, and it is possible, in multiple sclerosis, that remyelination may be promoted. 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 therapeutic 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
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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 pre-natal 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 immunoglobulin 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 al38), 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 1 diabetes mellitus).
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