

# Pregnancy and the Immune System in MS

Multiple sclerosis (MS) is a demyelinating disorder of the central nervous system that typically begins in young adults and affects women twice as often as men.<sup>1,2</sup> As MS is more prevalent in women of childbearing age than in other populations, it is important that neurologists be aware of the effect of pregnancy on the course of MS and have the most current information on the management of MS during pregnancy.<sup>3</sup> This information is essential in order to work in concert with the patient and her obstetrician-gynecologist to make clinical decisions. It is also necessary for accurate counseling of patients who are considering becoming pregnant.

## MS Disease Course During Pregnancy and the Puerperium

Before the 1950s it was generally believed that pregnancy had an adverse effect on the course of MS. In some cases termination of pregnancy was even recommended.<sup>4</sup> Subsequent studies found no difference in overall disease course between women with MS who became pregnant and those who did not.<sup>4</sup> However, both retrospective

and prospective studies have shown a reduction in relapse rate during pregnancy, followed by an increase in relapse rate during the postpartum period.<sup>5</sup>

For example, the 1998 Pregnancy in Multiple Sclerosis (PRIMS) study evaluated 254 women with MS who were followed during pregnancy and for up to 12 months after delivery.<sup>6</sup> Results showed that the relapse rate decreased about 70% by the third trimester of pregnancy, then increased about 70% during the first 3 months after delivery (Table 1).<sup>6</sup> This postpartum increase was greater than that seen after viral illness in men and women with MS.<sup>7</sup> However, there was no apparent effect on the overall rate of disease progression during the 33 months of the study period, as assessed by the Expanded Disability Status Scale (EDSS).<sup>6</sup>

Changes in maternal immunity may help to explain the alteration in relapse rate seen during and after pregnancy. Symptoms associated with autoimmune disorders may change for the better or worse during pregnancy. Symptoms improve during pregnancy for women with cell-mediated autoimmune disorders, such as rheumatoid arthritis, and worsen during pregnancy for women

**Table 1. MS relapse rates and pregnancy**

	Annual Relapse Rate	P Value*
Year before pregnancy	0.7	—
First trimester	0.5	0.03
Second trimester	0.6	0.17
Third trimester	0.2	<0.001
1–3 months postpartum	1.2	<0.001
4–6 months postpartum	0.9	0.17
7–9 months postpartum	0.9	0.15
10–12 months postpartum	0.6	0.59

\*Compared with the relapse rate during the year before pregnancy. MS, multiple sclerosis.

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with antibody-mediated autoimmune disorders, such as systemic lupus erythematosus.<sup>8</sup>

During pregnancy there appears to be a shift from a predominance of T<sub>H</sub>1 cells to T<sub>H</sub>2 cells.<sup>8</sup> This shift appears to revert back during the postpartum period to the prepregnancy state. These shifts may well contribute to the changes in MS relapse rate seen during pregnancy and the postpartum period, as MS is believed to involve myelin-sensitized T<sub>H</sub>1 cells that secrete proinflammatory cytokines.<sup>9</sup> The shifts may be advantageous from an evolutionary standpoint, because they reduce the risk of T<sub>H</sub>1-mediated rejection of the fetus as a foreign body.<sup>10</sup>

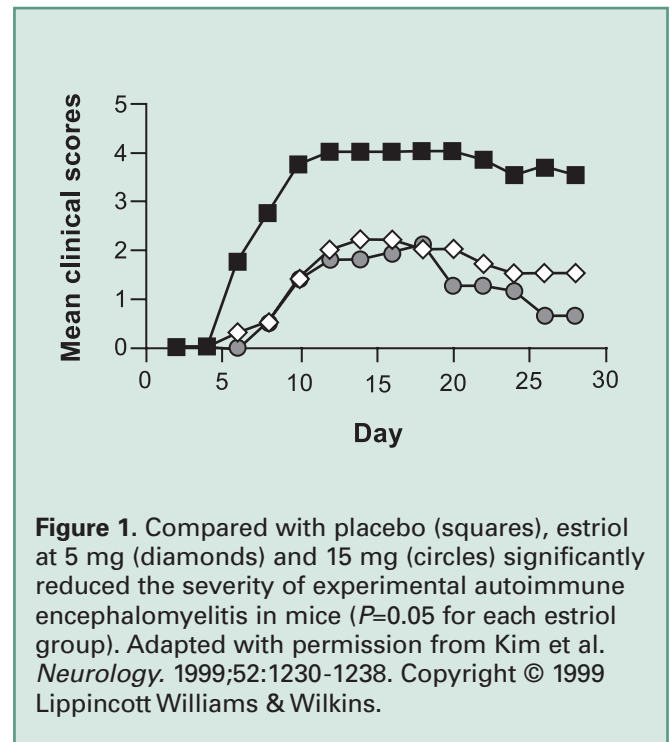
Because of the improvement in MS relapse rate seen during pregnancy, researchers have investigated the therapeutic use of pregnancy hormones to mimic the pregnant state in MS. For example, estriol, an estrogen produced by the fetal placental unit that is not present in the nonpregnant state, has been studied in both murine models of MS and humans. In mice with experimental autoimmune encephalomyelitis, estriol was found to significantly reduce the severity of disease compared with placebo (Figure 1).<sup>11</sup> In a small pilot study in nonpregnant women with MS, estriol was found to decrease gadolinium-enhancing lesions on magnetic resonance imaging (MRI).<sup>12</sup> When estriol treatment was stopped the lesions increased to pretreatment levels, but upon reinstatement of therapy they again decreased significantly. Additional research is needed with larger human studies, but these preliminary results suggest that mimicking the pregnant state offers a potential therapeutic intervention for patients with MS and other T<sub>H</sub>1-mediated autoimmune disorders.

### Risks of Pregnancy and MS

Women with MS who are pregnant or contemplating pregnancy may have concerns about the effect of pregnancy on the long-term course of MS. Few long-term studies have been performed. A retrospective study found no association between disability, and total number or timing of pregnancies relative to MS onset.<sup>13</sup> There was also no association between disability, and onset or worsening of MS during pregnancy.

In a 1994 study of 39 Danish women with MS followed for 5 years, there was no evidence that pregnancy worsened the course of disease.<sup>14</sup> However, the study was limited by its small size and dated in that immunomodulator therapy was not widely used at the time.

There is no evidence to suggest that MS affects fertility or leads to pregnancy loss or congenital malfor-



**Figure 1.** Compared with placebo (squares), estriol at 5 mg (diamonds) and 15 mg (circles) significantly reduced the severity of experimental autoimmune encephalomyelitis in mice ( $P=0.05$  for each estriol group). Adapted with permission from Kim et al. *Neurology*. 1999;52:1230-1238. Copyright © 1999 Lippincott Williams & Wilkins.

mations.<sup>3,15</sup> There is also no evidence of an increased incidence of preeclampsia, prematurity, or infant mortality.<sup>4</sup> A 3-year prospective study found no difference in head circumference or weight between infants whose mothers had MS and those whose mothers did not.<sup>16</sup>

In general, women with MS can expect a pregnancy that is similar to that in women without MS. However, women with gait disturbances may experience greater difficulty during late pregnancy as their weight increases and their center of gravity changes. During pregnancy, women with MS may also experience an increase in bowel and bladder problems and in fatigue. In addition, spinal anesthesia during labor and delivery may be less preferable than epidural or regional blocks.<sup>17,18</sup>

Women with MS may also be concerned about the safety of imaging during pregnancy. Although there are no data about the safety of MRI, there are no reports of fetal abnormalities associated with MRI scanning.<sup>5</sup> MRI should be used only when its outcome will change a patient's treatment plan.

Although pregnancy for women with MS is similar to that for women without MS, the postpartum period may be more difficult because of MS-related symptoms and the increased risk of relapse. One study found that 30% of women with MS had difficulty caring for their infants because of limb weakness or gait disturbances.<sup>19</sup> In addition, individuals with MS who experience fatigue during the postpartum period may need additional help with child care.

There are no contraindications to breast-feeding unless the mother is taking drugs that are toxic to the infant.<sup>4</sup> One retrospective study of more than 400 women with MS found no association between postpartum relapse rate and breast-feeding.<sup>20</sup> There is even some evidence to suggest that breast-feeding may improve MS status. One study found that subjects who breast-fed had slower progression of MS than did nonnursing mothers.<sup>21</sup> A more recent study documented no significant differences in rate of relapse between women who breast-fed in the year after pregnancy and those who did not, but when the entire 33-month study period was evaluated, a significantly lower rate in the breast-feeding mothers was observed.<sup>6</sup>

### Treatment Issues During Pregnancy and the Puerperium

Both patients with MS and their neurologists may be concerned about the need for alterations in treatment during pregnancy and the puerperium. Ordinarily, early initiation of immunomodulator therapy is recommended for relapsing MS.<sup>22</sup> In addition, mitoxantrone, an immunosuppressant, is indicated for secondary progressive, progressive relapsing, or worsening relapsing MS.<sup>23</sup> As with all pharmacologic therapies, however, the potential benefit to the mother must be weighed against the potential risk to the fetus.

The  $\beta$ -interferons (Avonex<sup>®</sup>, Betaseron<sup>®</sup>, and Rebif<sup>®</sup>) are designated by the Food and Drug Administration as Pregnancy Category C, since there is evidence of an abortifacient effect on pregnancy in animals. No well-controlled studies of the use of these agents in pregnant women have been performed.<sup>24-26</sup> Glatiramer acetate (Copaxone<sup>®</sup>) is designated as Pregnancy Category B, indicating that available animal studies have not shown a risk to the fetus, but again, there are no adequate studies in pregnant women.<sup>27</sup>

A case series presented at the annual meeting of the European Neurological Society in 2001 reported that there were no developmental abnormalities in infants of 11 women who elected to remain on a  $\beta$ -interferon or glatiramer acetate during pregnancy.<sup>28</sup> In addition, a recent retrospective review was conducted of 21 trials involving glatiramer acetate and of post-marketing surveillance data.<sup>29</sup> [Note: *This review was performed by Patricia K. Coyle, MD, the editor-in-chief of this publication.*] There were 30 pregnancies with known outcomes in the approximately 2,400 female patients receiving glatiramer acetate in the clinical trials. Of these, 6 had healthy full-term infants, 5 had sponta-

neous abortions, 18 had elective abortions, and 1 delivered an infant with cleft lip that was believed to have been caused by carbamazepine use. The post-marketing surveillance data showed that of the 215 pregnancies that had occurred while women were taking glatiramer acetate and for which data were available (of a total of 345 pregnancies), 72% resulted in a healthy full-term infant, 21% in spontaneous abortion, 3% in an infant with a congenital anomaly, and 4% in elective abortion. The most common adverse event in both data collections was spontaneous abortion, which occurred at a rate similar to that in an age-adjusted general population. These preliminary data suggest that use of immunomodulator therapy, particularly glatiramer acetate, is not associated with an increase in adverse events during pregnancy. More data are needed to confirm these results, especially as interferons are known to inhibit cell division, which theoretically could be a reason to avoid fetal exposure to them.

There is sufficient evidence to indicate mitoxantrone should be avoided during pregnancy. Mitoxantrone (Novantrone<sup>®</sup>) has been assigned a Pregnancy Category of D because of evidence of human fetal risk.<sup>23</sup> Women who are taking mitoxantrone should be warned to avoid becoming pregnant.

Given the abundance of evidence for an increased relapse rate during the postpartum period, patients with MS and their neurologists may consider changes to the treatment regimen during this period. Intravenous immunoglobulin (IVIG) may be useful. A pilot study conducted in 1996 found that IVIG was effective in preventing childbirth-associated relapse in women who had experienced relapses after previous pregnancies.<sup>30</sup> Another small study found that IVIG prevented postpartum relapse in the 14 women who received it after delivery.<sup>31</sup> Finally, a recent European study has found that women treated with IVIG had a relapse rate that was 33% lower than that seen after delivery in the PRIMS study.<sup>32</sup>

### Summary

MS tends to affect women of childbearing age. Women with MS may have concerns about both the effect of pregnancy on the course of MS and the effect of MS on the course of pregnancy. Current evidence suggests that pregnancy causes a reduction in relapse rate, especially during the third trimester, with a subsequent increase in relapse rate immediately postpartum. However, there is no evidence that pregnancy has long-term detrimental effects on the course of MS. Women with MS appear to

have similar experiences with pregnancy to those of women without MS, with the possible exception of an increased need for assistance with infant care during the postpartum period. Preliminary data suggest that immunomodulators (particularly glatiramer acetate) may be safe during pregnancy, but that the immunosuppressant mitoxantrone should not be used. The use of IVIG to prevent the increase in relapse rate seen in the puerperium is being investigated. Neurologists should familiarize themselves with information about pregnancy and MS, so that they may provide accurate information for their patients with MS who are pregnant or contemplating pregnancy.

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