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## RATE OF PREGNANCY-RELATED RELAPSE IN MULTIPLE SCLEROSIS

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### ABSTRACT

**Background and Methods** Multiple sclerosis often occurs in young women, and the effect of pregnancy on the disease is poorly understood. We studied 254 women with multiple sclerosis during 269 pregnancies in 12 European countries. The women were followed during their pregnancies and for up to 12 months after delivery to determine the rate of relapse per trimester and the score on the Kurtzke Expanded Disability Status Scale (range, 0 to 10, with higher scores indicating more severe disability). The relapse rate in each trimester was compared with the rate during the year before the pregnancy. The effects of epidural analgesia and breast-feeding on the frequency of relapse during the first three months post partum and the disability score at 12 months post partum were also determined.

**Results** The mean ( $\pm$ SD) rate of relapse was  $0.7 \pm 0.9$  per woman per year in the year before pregnancy; it was  $0.5 \pm 1.3$  during the first trimester ( $P=0.03$  for the comparison with the rate before pregnancy),  $0.6 \pm 1.6$  during the second trimester ( $P=0.17$ ), and  $0.2 \pm 1.0$  during the third ( $P<0.001$ ). The rate increased to  $1.2 \pm 2.0$  during the first three months post partum ( $P<0.001$ ) and then returned to the prepregnancy rate. The mean Kurtzke disability score worsened by 0.7 point during 33 months of follow-up, with no apparent acceleration during the postpartum period. Neither breast-feeding nor epidural analgesia had an adverse effect on the rate of relapse or on the progression of disability in multiple sclerosis.

**Conclusions** In women with multiple sclerosis, the rate of relapse declines during pregnancy, especially in the third trimester, and increases during the first three months post partum before returning to the prepregnancy rate. (N Engl J Med 1998;339:285-91.)

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**M**ULTIPLE sclerosis affects 1 in 1000 people in Western countries,<sup>1</sup> mainly women in their childbearing years.<sup>2,3</sup> In general, the rate of relapse has been thought to decrease during pregnancy and increase in the postpartum period, but the studies have been small, and some have reached different conclusions.<sup>4-9</sup> The Pregnancy in Multiple Sclerosis (PRIMS) study was a European multicenter, prospective, observational study designed to determine the effect of pregnancy and the postpartum state on the course of the disease, along with that of breast-feeding and epidural analgesia.

### METHODS

#### Study Design and Recruitment of Subjects

We studied 254 women with multiple sclerosis that began before the pregnancy under study and that was diagnosed according to the classification of Poser et al.<sup>10</sup> This classification scheme for the degree of certainty regarding the diagnosis combines three criteria: dissemination of lesions in time; dissemination of lesions in space, evidence of which may be clinical or paraclinical (from evoked potentials, computed tomography, or magnetic resonance imaging); and quantitative or qualitative abnormalities in immunoglobulins in the cerebrospinal fluid. Clinically definite cases are defined by dissemination in time and space, regardless of the results of cerebrospinal fluid tests; laboratory-supported definite cases are defined by dissemination in time and cerebrospinal fluid abnormalities, or by dissemination in space and cerebrospinal fluid abnormalities; clinically probable cases are defined only by dissemination in time or space; laboratory-supported probable cases by cerebrospinal fluid abnormalities only; and suspected cases by the lack of fulfillment of any of the three criteria.

All the women had been pregnant for at least 4 weeks but less than 36 weeks at entry into the study. Any European neurologist willing to participate in the study was invited to do so and received

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the study protocol and data-collection forms designed for use with the European Database for Multiple Sclerosis (EDMUS) system.<sup>11</sup>

Recruitment of the women began in January 1993 and ended when the target number of 250 pregnancies was reached in July 1995. This number was calculated to allow the study to detect a reduction of at least 33 percent in the relapse rate during the third trimester of pregnancy, as compared with the rate during the year before pregnancy. A total of 194 of the women (76 percent) were known to the study neurologist before the pregnancy. The study protocol was approved by the ethics committee of St. Vincent's Hospital, Dublin, Ireland, and all the women gave informed consent.

### Assessment of Subjects

After enrollment, the women were examined at 20 and 28 weeks of gestation if enrollment took place before those times. In any case, all the women were examined at 36 weeks of gestation, and they were assessed by telephone at 40 weeks. Subsequently, they were examined 3, 6, and 12 months post partum, with telephone assessments 1 and 9 months post partum. For each woman, the same neurologist conducted all evaluations and completed a standardized form on each occasion. Short courses of glucocorticoids were the only immunologic treatment for multiple sclerosis allowed during pregnancy.

We recorded obstetrical data on previous pregnancies and their outcomes, the date of the last menstrual period, any complications of the pregnancy under study, the method of delivery and any complications, the use or nonuse of epidural analgesia, whether the mother was breast-feeding her infant, and the weight, sex, and health status of the infant.

The following data were collected on the course of multiple sclerosis: date of onset, total number of relapses before the study pregnancy, number of relapses in the year before the study pregnancy, number of relapses during the study pregnancy but before enrollment in the study, whether the course was relapsing–remitting or progressive,<sup>2,11</sup> and the extent of neurologic disability one year before the last menstrual period before the study pregnancy and at the beginning of the pregnancy.

We also collected the following prospective data: extent of neurologic disability at the time of enrollment in the study, at 36 weeks' gestation, and 3, 6, and 12 months post partum; whether there was any new relapse; and any immunologic treatments, such as glucocorticoids and immunosuppressant or immunomodulating drugs. For the women who became pregnant again less than a year after the first pregnancy, the study period for the first pregnancy was defined as ending at the time of the last menstrual period before the second pregnancy.

Once completed by the neurologist, the data-collection forms were sent to the coordinating center, where the staff ensured that the data were internally consistent and that follow-up was on schedule. Any inconsistencies were pointed out by the staff, and further information was sought from the neurologist. All the data received at the coordinating center were sent back to the neurologist for final validation.

A relapse of multiple sclerosis was defined as the appearance or worsening of symptoms of neurologic dysfunction lasting more than 24 hours. Fatigue alone was not considered a relapse. Neurologic disability was assessed with use of the Kurtzke Expanded Disability Status Scale,<sup>12</sup> which is based on the data from the neurologic examination and the patient's ability to walk. Scores range from 0 (indicating no neurologic abnormality) to 10 (death caused by multiple sclerosis). Residual neurologic disability was defined as the minimal level of persistent disability recorded on two consecutive examinations at least three months apart, excluding any transient worsening of disability related to relapses.

### Statistical Analysis

The rates of relapse per woman per year during each three-month period during pregnancy and the postpartum year were compared with the relapse rate during the year before the preg-

nancy began by means of paired, two-sided t-tests. The effects of epidural analgesia and breast-feeding on the course of multiple sclerosis were analyzed by logistic-regression analysis, with adjustment for age and the duration of disease at the beginning of pregnancy and the occurrence of relapses, for each three-month period during the year before the pregnancy and during pregnancy. One outcome analyzed was the occurrence of a relapse during the first three months post partum; the second was an increase of 1.0 point or more in the residual Kurtzke score as determined at the beginning of pregnancy and the end of the postpartum year. Finally, the method of Wei and Johnson was used to calculate an overall P value for the association of the relapse rates and residual disability with either epidural analgesia or breast-feeding during the entire 33-month study period from 1 year before the pregnancy began to the 12th month post partum.<sup>13</sup> All computations were performed with SPSS for Windows software, version 6.1.<sup>14</sup>

## RESULTS

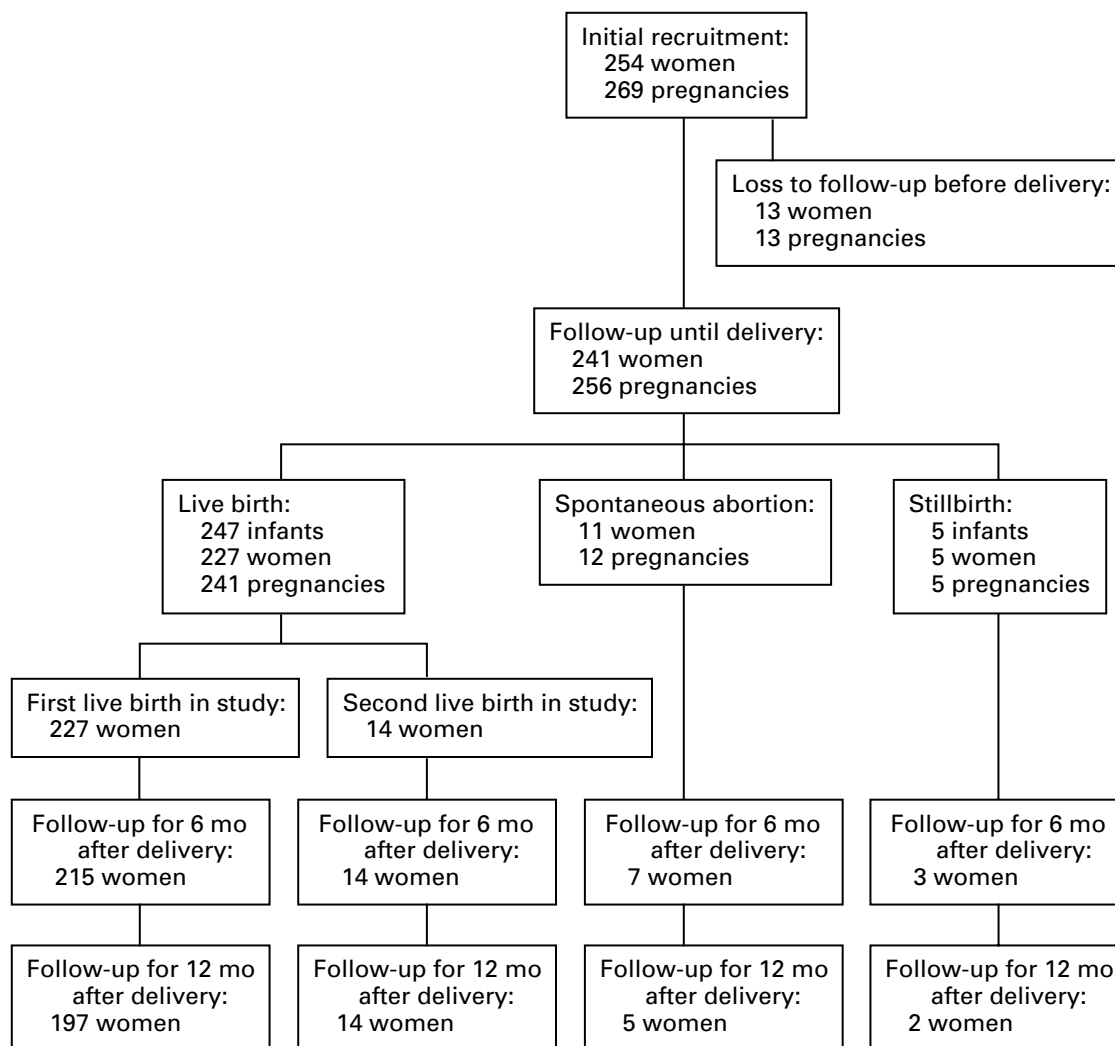
### Characteristics of the Women with Multiple Sclerosis

A total of 254 women were enrolled in the study (Fig. 1). Fifteen were studied during 2 pregnancies, for a total of 269 study pregnancies. The last delivery took place in February 1996. The base-line characteristics of the 254 women are shown in Table 1. Among the 241 full-term pregnancies, the mean ( $\pm$ SD) duration of the pregnancy at the time of enrollment was  $18\pm 9$  weeks; 113 of the 241 women (47 percent) were enrolled during the first trimester, 93 (39 percent) during the second trimester, and 35 (15 percent) during the third trimester. Sixteen women received glucocorticoid therapy during pregnancy. During the first six months after delivery, 35 women received glucocorticoid therapy, 4 received azathioprine, and 1 received mitoxantrone; during the second six months post partum, 27 women received glucocorticoid therapy, 3 azathioprine, 6 recombinant interferon beta-1b, 1 mitoxantrone, and 1 cyclophosphamide.

### Outcomes of Pregnancy

Full data on pregnancy and delivery were available for 256 pregnancies in 241 women (Fig. 1). Among the 241 full-term pregnancies (227 first pregnancies and 14 second pregnancies), there were 8 twin pregnancies; 2 of these resulted in the delivery of one still-born and one live infant. The mean duration of pregnancy was  $39\pm 3$  weeks; 27 pregnancies ended at or before 36 weeks. Among the live-born infants, there were 130 boys and 113 girls (for 4 infants, the sex was not recorded). The mean weight at delivery was  $3.3\pm 0.6$  kg; seven infants weighed less than 2.5 kg. One infant had ureteral stenosis with mild hydronephrosis. All the live-born infants were healthy at one year of age, except for one twin who died of sudden infant death syndrome at the age of three months.

There were 196 vaginal deliveries and 43 cesarean deliveries (data were missing in 2 cases). Epidural analgesia was given to 42 women. There were few complications during or after delivery. One woman had eclampsia; 12 had excessive bleeding, of whom



**Figure 1.** Outcomes of Pregnancy and Follow-up in Women with Multiple Sclerosis Who Were Recruited into the Study. Eight women were pregnant with twins; in two cases, one twin was born alive and one was stillborn (these women and pregnancies appear twice in the figure).

only 5 required blood transfusion, and 9 had infection. Among the 209 women for whom information was available, 122 chose to breast-feed their infants.

**Relapses of Multiple Sclerosis**

For each woman, only the first pregnancy during the study that led to a live birth was included in our analyses. This amounted to a total of 227 pregnancies. The relapse rates for each three-month period during the year before the pregnancy, during the pregnancy, and during the postpartum year are shown in Table 2 and Figure 2. As compared with the prepregnancy year, in which the mean rate of relapse was  $0.7 \pm 0.9$  per woman per year, the relapse rates in the first and the second trimesters of pregnancy were slightly lower, and that during the last trimester was

substantially lower ( $0.2 \pm 1.0$  relapse per woman per year). After delivery, the rate during the first three months was higher than that before pregnancy, but in the second, third, and fourth three-month periods it was similar to the rate before pregnancy.

Table 3 shows the relapse rates during the study period according to whether the women received epidural analgesia and breast-fed their infants. The risk of a relapse after delivery was not affected by the use of epidural analgesia (odds ratio as compared with nonuse, 1.5; 95 percent confidence interval, 0.7 to 3.2;  $P=0.51$ ) or by breast-feeding (odds ratio as compared with not breast-feeding, 0.8; 95 percent confidence interval, 0.4 to 1.5;  $P=0.51$ ). When we evaluated the entire 33-month study period by the Wei-Johnson method,<sup>13</sup> there was no significant difference in the rate of relapse between women who

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE 254 WOMEN WITH MULTIPLE SCLEROSIS, ACCORDING TO OUTCOMES OF PREGNANCY.\***

CHARACTERISTIC	LIVE BIRTH	ABORTION OR STILLBIRTH	LOSS TO FOLLOW-UP BEFORE DELIVERY
No. of women	227	14	13
Age at beginning of pregnancy — yr	30±4	30±3	32±4
Duration of multiple sclerosis before pregnancy — yr	6±4	6±5	8±5
No. of relapses before pregnancy	4±4	4±2	6±4
Residual Kurtzke disability score at beginning of pregnancy†	1.3±1.4	1.0±1.1	2.1±1.6
Course at enrollment — no. (%)‡			
Relapsing–remitting	219 (96)	14 (100)	13 (100)
Secondary progressive	8 (4)	0	0
Primary progressive	0	0	0
Degree of diagnostic certainty — no. (%)§			
Clinically definite	70 (31)	3 (21)	3 (23)
Laboratory-supported definite	52 (23)	4 (29)	2 (15)
Clinically probable	63 (28)	5 (36)	4 (31)
Laboratory-supported probable	16 (7)	0	4 (31)
Suspected	26 (11)	2 (14)	0

\*Plus–minus values are means ±SD. If a woman had two pregnancies during the study period, only the first pregnancy is included in this analysis.

†The score on the Kurtzke Expanded Disability Status Scale<sup>12</sup> is based on data from the neurologic examination and the patient's ability to walk. It ranges from 0 (no neurologic abnormality) to 10 (death caused by multiple sclerosis). Residual disability was defined as the minimal level of persistent disability recorded on two consecutive examinations at least three months apart, excluding any transient worsening of disability related to relapses.

‡In the relapsing–remitting forms of multiple sclerosis, relapses are separated by periods of clinical inactivity and there is no progression (continuous worsening of symptoms and signs for a minimum of six months) between relapses. In the progressive forms, there is continuous worsening of symptoms and signs for a minimum of six months, whether or not there are relapses; clinical progression in multiple sclerosis can occur after an initial relapsing–remitting phase of the disease (secondary progressive forms) or from the clinical onset of the disease (primary progressive forms).<sup>11</sup>

§We used the classification of Poser et al.<sup>10</sup> to characterize the degree of certainty regarding the diagnosis of multiple sclerosis (see the Methods section).

**TABLE 2. RELAPSES OF MULTIPLE SCLEROSIS DURING PREGNANCY AMONG 227 WOMEN.**

PERIOD	NO. OF WOMEN*	NO. OF RELAPSES	RATE OF RELAPSE/WOMAN/YR†	P VALUE‡
Year before pregnancy				
Months 1–3	227	36	0.6 (0.5–0.7)	
Months 4–6	227	41	0.7 (0.6–0.8)	
Months 7–9	227	42	0.7 (0.6–0.9)	
Months 10–12	227	45	0.8 (0.7–0.9)	
Months 1–12	227	164	0.7 (0.6–0.8)	
Pregnancy				
First trimester	227	27	0.5 (0.4–0.6)	0.03
Second trimester	227	32	0.6 (0.5–0.7)	0.17
Third trimester	225	12	0.2 (0.2–0.3)	<0.001
Year after pregnancy				
Months 1–3	222	68	1.2 (1.1–1.4)	<0.001
Months 4–6	215	47	0.9 (0.8–1.0)	0.17
Months 7–9	204	46	0.9 (0.8–1.0)	0.15
Months 10–12	197	31	0.6 (0.5–0.7)	0.59

\*The numbers shown are the numbers of women who were followed for the entire three-month period. Only relapses in these women have been considered.

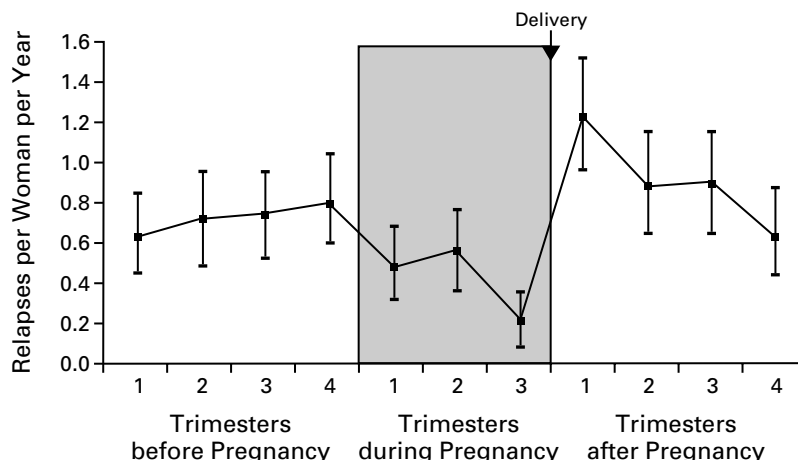
†Values are means and 95 percent confidence intervals.

‡P values are for the comparison with the relapse rate during the year before pregnancy.

underwent epidural analgesia and those who did not (P=0.54). By contrast, women who breast-fed their infants had a significantly lower rate of relapse than women who did not (P=0.02).

**Disability Related to Multiple Sclerosis**

The residual Kurtzke disability score worsened steadily during the study, with a mean increase of 0.7 by the end of the 33-month study period (Table 4). There was no apparent acceleration of the progression of disability in the postpartum period as compared with the earlier periods, either among all the women or in subgroups defined according to whether they had received epidural analgesia (odds ratio, 1.1; 95 percent confidence interval, 0.5 to 2.6; P=0.80) or whether they had breast-fed their infants (odds ratio, 1.4; 95 percent confidence interval, 0.7 to 3.0; P=0.27). When analyzing the entire 33-month study period by the method of Wei and Johnson,<sup>13</sup> we did not find any significant difference in the progression of disability according to the use or nonuse of epidural analgesia (P=0.66) or whether women breast-fed their infants (P=0.27).



**Figure 2.** Rate of Relapse per Woman per Year for Each Three-Month Period before, during, and after Pregnancy in 227 Pregnancies Resulting in a Live Birth among Women with Multiple Sclerosis. The values shown are means and 95 percent confidence intervals.

**TABLE 3.** RATE OF RELAPSE AMONG WOMEN WITH MULTIPLE SCLEROSIS IN RELATION TO THE USE OR NONUSE OF EPIDURAL ANALGESIA AND WHETHER OR NOT THE WOMEN BREAST-FED THEIR INFANTS.\*

PERIOD	EPIDURAL ANALGESIA		BREAST-FEEDING	
	YES (N=42)	NO (N=180)	YES (N=122)	NO. (N=87)
	no./woman/yr (95 percent CI)			
Year before pregnancy	0.7 (0.4-1.0)	0.7 (0.6-0.8)	0.6 (0.5-0.7)	0.8 (0.6-1.0)
Pregnancy	0.5 (0.3-0.7)	0.4 (0.3-0.5)	0.3 (0.2-0.4)	0.5 (0.3-0.7)
Year after pregnancy				
Months 1-3	1.6 (0.9-2.3)	1.2 (1.0-1.4)	1.2 (0.9-1.4)	1.3 (1.0-1.6)
Months 4-6	1.0 (0.1-2.0)	0.9 (0.7-1.1)	0.9 (0.6-1.1)	1.0 (0.7-1.3)
Months 7-9	0.7 (0.3-1.2)	0.9 (0.7-1.1)	0.8 (0.6-1.1)	1.0 (0.7-1.3)
Months 10-12	0.7 (0.2-1.1)	0.6 (0.4-0.8)	0.6 (0.4-0.8)	0.8 (0.5-1.0)

\*The values shown are the mean number of relapses per woman per year, with 95 percent confidence intervals (CI). Only women for whom data on epidural analgesia or breast-feeding were available are included.

**DISCUSSION**

In this large prospective study of the natural history of multiple sclerosis in pregnant women, the frequency of relapses of multiple sclerosis decreased during pregnancy, particularly during the third trimester, and increased in the first three months post partum, as compared with the rate during the year before pregnancy. The women served as their own controls, because matching a cohort of pregnant women with multiple sclerosis with a cohort of women with multiple sclerosis who did not become pregnant has proved difficult. The decision of a woman with multiple sclerosis to become pregnant is strongly influenced by disease activity.

Although the study formally began when the women were pregnant, 52 percent had been followed prospectively by the participating neurologist before pregnancy. If the study had begun a year before the

pregnancy began, the relapse rate for the prepregnancy year would probably have been higher, and consequently the reduction in the relapse rate during pregnancy would have been greater. Furthermore, in other studies, the mean relapse rate in young women with multiple sclerosis has been at least 0.5 per woman per year.<sup>2,3</sup> The ability to detect relapses is a function of the frequency of evaluation.<sup>15</sup> For that reason, given a mean relapse rate of 0.7 per year for the year before pregnancy, detection of relapses during this period was probably adequate.

Most previous studies of the effect of pregnancy on the frequency of relapse in women with multiple sclerosis have been retrospective or cohort studies; one prospective study was of eight women.<sup>16</sup> In many of the older studies,<sup>17-21</sup> the relapse rate was less than 0.5 per year, suggesting inadequate retrospective review, and in only one<sup>22</sup> were the results similar to

**TABLE 4.** RESIDUAL KURTZKE DISABILITY SCORE BEFORE, DURING, AND AFTER PREGNANCY AMONG 227 WOMEN WITH MULTIPLE SCLEROSIS.\*

SCORE	1 Yr BEFORE PREGNANCY	AT BEGINNING OF PREGNANCY	AT DELIVERY	6 Mo POST PARTUM†	1 Yr POST PARTUM‡
	number of women (percent)				
0	77 (34)	65 (29)	45 (20)	39 (18)	30 (15)
1	77 (34)	83 (37)	103 (45)	94 (44)	82 (42)
2	24 (11)	31 (14)	36 (16)	37 (17)	39 (20)
3	10 (4)	15 (7)	15 (7)	18 (8)	13 (7)
4	10 (4)	13 (6)	16 (7)	11 (5)	14 (7)
5	1 (<1)	1 (<1)	8 (4)	10 (5)	9 (5)
6	0	1 (<1)	2 (1)	4 (2)	4 (2)
7	0	0	0	0	1 (<1)
8	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)
Unknown	26 (11)	16 (7)	0	0	3 (2)
<b>GROUP OF WOMEN</b>					
	mean score ±SD				
All women	1.1±1.3	1.3±1.4	1.6±1.5	1.7±1.5	1.8±1.6
Epidural analgesia					
Yes (n=42)	1.0±1.1	1.2±1.2	1.5±1.4	1.6±1.5	1.7±1.5
No (n=180)	1.1±1.4	1.3±1.4	1.5±1.5	1.7±1.6	1.7±1.6
Breast-feeding					
Yes (n=122)	1.0±1.1	1.2±1.2	1.5±1.3	1.6±1.4	1.7±1.4
No (n=87)	1.2±1.6	1.3±1.6	1.6±1.7	1.8±1.8	1.8±1.8

\*The score on the Kurtzke Expanded Disability Status Scale<sup>12</sup> is based on data from the neurologic examination and the patient's ability to walk. It ranges from 0 (no neurologic abnormality) to 10 (death caused by multiple sclerosis). Residual disability was defined as the minimal level of persistent disability recorded on two consecutive examinations at least three months apart, excluding any transient worsening of disability related to relapses. Because of rounding, not all percentages total 100.

†This analysis includes 215 women; 8 had been lost to follow-up, and 4 were pregnant again.

‡This analysis includes 197 women; 19 had been lost to follow-up, and 11 were pregnant again.

those reported here. In the six more recent studies,<sup>16,22-26</sup> which enrolled a total of 203 women in whom the relapse rates when they were not pregnant were more than 0.5 per year, the pooled results are in agreement with ours.

The overall rate of progression of disability did not change during the study period, despite the increase in the relapse rate in the first three months post partum. The mean increase in the residual Kurtzke score for the entire 33-month study period was 0.7, a value within the expected range of what is known about the natural history of multiple sclerosis in women with minimally disabling disease.<sup>3</sup> We also found that epidural analgesia and breast-feeding did not increase the risk of relapse or of worsening disability in the postpartum period; this finding agrees with those of another study.<sup>21</sup> Our results are also in accord with studies that have shown that multiple sclerosis does not seem to have a deleterious effect on the course and outcome of pregnancy or delivery.<sup>9,16,24-29</sup>

The decrease in the relapse rate during pregnancy was more marked than any therapeutic effect reported to date.<sup>30-33</sup> This clinical observation is corroborated by the cessation of disease activity on magnetic reso-

nance imaging during the third trimester of pregnancy.<sup>34</sup> From an immunologic point of view, normal pregnancy seems to be associated with a shift away from cell-mediated immunity toward increased humoral immunity.<sup>35</sup> The fetal-placental unit secretes cytokines such as interleukin-10 that down-regulate the production of other cytokines mediating cellular immunity by the mother. This cell-mediated immunodepression could explain the tolerance of the fetus by the mother. In contrast, delivery might be associated with an inversion of this cytokine balance and could be regarded, in some respects, as a graft-rejection process.<sup>35</sup>

This concept could explain why pregnancy is associated with spontaneous remission and the postpartum period with exacerbations in T-cell-mediated autoimmune diseases such as multiple sclerosis and rheumatoid arthritis.<sup>36</sup> Conversely, B-cell-mediated autoimmune diseases, such as systemic lupus erythematosus, tend to worsen during pregnancy.<sup>37</sup> A better understanding of the biologic mechanisms underlying this pregnancy-related decrease in disease activity could lead to new and effective therapeutic strategies in multiple sclerosis.

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APPENDIX

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