In this issue of *Neurology®*, Benoit et al. describe results of a multicenter collaborative study designed to identify the association between relapses in the periods before, during, and after 2 successive pregnancies in women with multiple sclerosis (MS). MS is the leading cause of chronic neurologic disability in young adults worldwide, and because it disproportionately affects women of childbearing age, issues associated with pregnancy are of great importance to patients and their health care providers. Pregnancy is accompanied by a reduction in annualized relapse rates (ARRs), followed by an increased risk for relapses in the postpartum period (reviewed in Vukusic and Marignier). It is unlikely that MS hampers either fertility or pregnancy outcome and hence multiple pregnancies among patients with MS is a common and often-desired scenario. Naturally, the potential for relapse after delivery is of concern to patients who wish to plan additional pregnancies. To evaluate MS disease activity in multiple pregnancies, Benoit and collaborators analyzed relapse data in a cohort of patients (n = 93) who had at least 2 successive pregnancies during a 10-year period from 1993 to 2013. Demographic, disease, and pregnancy-specific data were available from 1 French and 4 Italian MS centers participating in the European Database for Multiple Sclerosis (EDMUS; France) and the iMed database (Merck Serono-Geneva; Italy). As a possible control for disease severity, 68 French patients who had only 1 pregnancy during the study period were also included.

Analyses for both pregnancies confirmed prior observations that ARRs are reduced during pregnancy, and importantly, that no difference was found between the first and second pregnancies. For the postpartum period, the increase in relapse frequency did not differ after the second pregnancy compared with the first. Twenty-nine of 93 women (31.2%) experienced a relapse in the first 3 months after the first pregnancy, and only 7 of these patients (7.6%) also had a relapse after the second pregnancy. However, the fact that 15 women with no postpartum relapse after the first pregnancy experienced a relapse after the second pregnancy indicates that the occurrence of postpartum relapses after the first pregnancy could not be identified as a predictor of relapses in the second postpartum period. No other measures, including relapses prior to or during the first pregnancy, or use of disease-modifying treatments in the year prior to pregnancy, were identified as predictors of relapses after the second pregnancy. This may reflect the small size of the study or a bias toward individuals with milder disease prior to pregnancy, a persistent problem with studies of MS and pregnancy. The potential bias for milder disease in the cohort is supported by the finding that the control group of 68 French patients who had only 1 pregnancy exhibited more active disease before pregnancy. Differences in patient age and exposure to disease-modifying treatments between French and Italian sites may have also influenced the power to identify clear clinical predictors of postpartum relapse activity.

What does this mean for counseling women with MS who wish to expand their families? The authors suggest, and the data support, that counseling for a second pregnancy should be the same as for the first one, and should include information about both the protective effects of pregnancy and the risks for relapse in the first 3 months after delivery. The authors specifically mention that the majority (70–80%) of patients do not experience relapses after delivery. This point is often neglected in discussions because of the justified concern for any risk of postpartum relapse.

What does this mean for future studies of pregnancy and MS? One can think of pregnancy and the postpartum periods as unique experiments of nature, rich with potential to yield new insights into the evolution of clinical disease and into mechanisms of disease pathogenesis. In spite of numerous studies conducted over approximately the last 2 decades since the hallmark Pregnancy in MS (PRIMS) study was published in 1998, many questions remain, especially, but not restricted to, safe timing and choices of disease-modifying drugs before and after pregnancy, and conflicting reports on the effects of...
breastfeeding on postpartum relapse risk. There is a clear need for prospective, longitudinal international registries designed to capture comprehensive information on disease activities relative to factors associated with pregnancy planning, pregnancy itself, and the postpartum period. Indeed, Alwan et al. reviewed existing treatment-specific, disease-specific, and MS-specific pregnancy registries and discussed the urgent need for development of a North American MS pregnancy registry to identify pregnancies and capture information about clinical disease, treatment, pregnancy, lactation, and offspring health.

To our knowledge, none of the existing pregnancy registries appear to include efforts to identify biomarkers for alterations in MS disease activity associated with pregnancy and the postpartum period. Pregnancy represents the ultimate state of immune regulation, induced by a unique combination of paternal antigens, hormones, and other factors to ward off rejection of an allogeneic fetus, while still providing protective immunity for both mother and fetus. Changes in innate and adaptive immune mechanisms that reflect specialized events during each trimester, such as fertilization, implantation, placentation, fetal growth, and preparation for parturition, seem likely to be involved in regulating MS-specific immune pathology. Similarly, the abrupt interruption of pregnancy-induced immune regulation initiated by parturition may promote proinflammatory mechanisms underlying clinical relapses. Indeed, pregnancy and the postpartum period can be considered models of remission and relapse in patients with MS disease activity associated with pregnancy and the postpartum period.

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