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The Role of Hormones in MS

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Two clinical observations related to hormonal influence and multiple sclerosis (MS) have sparked considerable research interest in this area: Young men are less susceptible to MS than young women, and there are fewer relapses in MS during the third trimester of pregnancy.

MALE SEX HORMONES

The lower susceptibility of young men to MS is consistent with observations in numerous other autoimmune diseases, including rheumatoid arthritis and lupus. Increased susceptibility in women as compared to men may be due to differences in sex hormones and/or sex chromosomes. Much research has focused on sex hormones, with very little research to date on sex chromosomes. With regard to sex hormones, the onset of MS in women is relatively younger than in men. Data in MS models[1–2] suggest that levels of circulating testosterone may be sufficiently high in some young males to protect from disease. Indeed, onset of MS in men generally occurs above the age of 30, and it is known that testosterone levels normally begin to decline by 1–2% per year beginning at the age of 30.[3–4] Also, two groups have found that testosterone levels are lower in some men with MS,[5–6] but whether this is the cause or the effect of the disease remains unknown. On the other hand, while males may be less susceptible to MS, there is some evidence that once disease begins, it may take a more aggressive course.[7] This possible sex-related difference in the severity of disease course remains to be fully characterized and its etiology is presently unknown.

FEMALE SEX HORMONES

While data are relatively clear that persistently high, young adult levels of male sex hormones are protective, such is not the case with female sex hormones, which fluctuate normally during the menstrual cycle. Unlike studies of the MS model in male mice, whereby castration clearly makes disease worse in males, it is controversial whether ovariectomy makes disease significantly worse in females, thereby making the role of fluctuating levels of estrogen and progesterone in cycling

females unclear. In MS patients who have had brain MRIs at various times during the menstrual cycle, there has been no consistent, significant correlation between disease activity and levels of estrogen or progesterone during the menstrual cycle.[8–9] Subjective premenstrual worsening of pre-existing MS symptoms has also been reported, but a clear association of this worsening with an increase in gadolinium enhancing lesions remains to be shown.[8,10] Furthermore, there is no evidence of increased relapses or an increase in enhancing lesions on MRI during menopause. Since women are generally in their early 50s during menopause—an age by which natural aging has decreased the frequency of relapses—an increase in relapses with menopause would have likely been recognized anecdotally. On the other hand, some women report feeling worse with menopause and better with hormone replacement therapy.[11] These subjective changes in symptoms with menopause may or may not be related to MS pathogenesis. If they are related to MS pathogenesis, they could involve factors such as disease-related cognitive changes, fatigue, and depression. A well-controlled study to assess these latter factors objectively in menopausal MS women, with more appropriate MRI measures such as atrophy accumulation or functional imaging, has not been done. In summary, low fluctuating levels of female sex hormones have not been shown to affect relapses or the appearance of new deficits, but an effect on pre-existing deficits cannot be ruled out at present.

THE IMPACT OF PREGNANCY ON RELAPSE RATE

It has been recognized for decades that symptoms of patients with autoimmune diseases are affected by pregnancy and the post partum period. The list of autoimmune diseases known to improve during pregnancy includes multiple sclerosis, rheumatoid arthritis, thyroiditis and uveitis. Early studies in MS did not separate the MS patients into relapsing remitting (RR) and secondary progressive (SP) groups.[12–14] What was generally described, however, was that there was a period of relative "safety" with regard to relapses during pregnancy, followed by a period of increased relapses post partum. These early clinical observations were supported by a small study of two patients who underwent serial brain MRIs during pregnancy and post partum. In both women there was a decrease in brain MRI disease activity during the second half of pregnancy and a return of disease activity to pre-pregnancy levels in the first months postpartum.[15] The most definitive study of the effect of pregnancy on MS came in 1998—the Pregnancy in Multiple Sclerosis (PRIMS) study.[16] Relapse rates were determined in 254 women with MS during 269 pregnancies, for up to one year after delivery. Relapse rates were significantly reduced from 0.7 per woman in the year before pregnancy to 0.2 during the third trimester (a 71% reduction). Rates then increased to 1.2 during the first three months post partum before returning to pre-pregnancy rates. No significant changes were observed between relapse rates in the first and second trimester as compared to the year prior to pregnancy. Together, these data clearly demonstrated that the latter part of pregnancy is associated with a significant reduction in relapses, while there is a rebound increase in relapses post partum.

PREDICTING POST PARTUM RELAPSES

In a recent follow-up report of the PRIMS study,[17] the authors attempted to predict which women would or would not relapse in the post partum period. This is important for private discussions between physicians and their patients about management of their pregnancy, as well as for MS researchers designing clinical trials of agents to prevent the post partum relapse. It was found that the most significant predictor of post partum relapses was the relapse rate prior to pregnancy; a woman who had active relapsing disease before becoming pregnant was more likely to have a relapse post partum than a woman whose pre-pregnancy relapse rate was lower. Neither epidural anesthesia nor breast feeding was predictive. A slight trend for fewer post partum relapses in women who breast fed was due to the fact that women who chose to breast feed had milder, less active disease before pregnancy as compared to those who chose not to breast feed. Thus, breast feeding itself was not directly related to post partum relapse; level of disease activity before pregnancy was determined to be the direct predictor.

EFFECT OF PREGNANCY ON DISABILITY

Since the third trimester of pregnancy is associated with a reduction in relapses and the postpartum period with an increase in relapses in the first three months, what is the net effect of pregnancy on the accumulation of disability? The net effect is controversial. The two-year post-partum analysis in the PRIMS study showed that disability continued to accumulate at a rate unaffected by pregnancy and the post partum period. However, two smaller studies followed patients for longer periods of time and found that the development of disability was reduced with pregnancy. Damek's studies suggested that a full-term pregnancy increased the time interval to reach a common disability endpoint (walking with the aid of a cane or crutch); in essence, pregnancy increased the time interval to having a secondary progressive course.[18] Runmarker found that there was a significantly decreased risk of a progressive course in women who became pregnant after multiple sclerosis onset as compared to those who did not.[19] In the latter study, patients were matched for neurologic deficit, disease duration and age. Matching was needed since one might predict that women with less disability would be more likely to get pregnant, hence a difference in baseline disability (not pregnancy) could explain the longer time interval to reach secondary progressive disease. Careful matching of the groups made this explanation unlikely and therefore this study provided some support for a net beneficial effect of pregnancy on the accumulation of disability in MS over the long term.

THE NET EFFECT OF PREGNANCY ON SUBSEQUENT RISK OF DEVELOPING MS

There appear to be no conclusive data supporting a long term effect of pregnancy in healthy individuals and their subsequent risk of developing MS. One study reported that women of parity 0–2 developed MS twice as often as women of parity 3 or more, thereby implying a protective effect of multiple pregnancies, but the difference did not reach statistical significance,[20] while another found no association between parity and the subsequent risk of developing MS.[21]

Together these data indicate that pregnancy in healthy women does not reduce their susceptibility to developing MS in the future.

On the other hand, if healthy women get pregnant, they are less likely to develop MS *during* pregnancy.[19] This is analogous to the observation that if women with MS get pregnant, it will indeed be associated with a temporary reduction in relapses *during* pregnancy, but not afterwards. The effect of pregnancy on relapses and new onset cases (first clinical episodes) appears to be similar to what is observed when patients take the approved immunomodulatory therapies for MS: relapse rate is temporarily reduced while patients are on the treatments but returns to the pre-medication rate when the medications are discontinued.

THE PREGNANCY FACTOR THAT IS TEMPORARILY PROTECTIVE

Pregnancy is a complex event that involves numerous changes. Leading candidate factors that may play a role in disease improvement include estrogens, progesterone, alpha-fetoprotein and vitamin D.[22] Two estrogens have been shown to be protective in animal models of MS when given in doses that achieve high levels equal to or greater than pregnancy. They include estradiol, the estrogen of the menstrual cycle, and estriol, an estrogen unique to pregnancy. Since estriol is not only the estrogen of pregnancy but has been known for over thirty years to be the safest of the estrogens,[23–26] it was administered in pill form in a pilot clinical trial to MS patients. Estriol treatment was shown to decrease gadolinium enhancing lesions in the brain of patients with relapsing-remitting MS (RRMS), as well as to have a favorable effect on immune responses.[27–28] Further trials of estriol treatment in RRMS are planned. Treatment with a combination of pregnancy factors is also an attractive idea to recapitulate the protection of pregnancy. These agents are primary candidates for use in trials to prevent the post partum relapse.

THE ESTROGENS IN ORAL CONTRACEPTIVES

Levels of estrogens that are lower than that which occurs during pregnancy—such as the levels induced by oral contraceptives (or hormone replacement therapy) may or may not be high enough to be protective in MS. It is not surprising that past use of oral contraceptives in healthy women was shown to have no effect on subsequent risk of developing MS[21] since one would not anticipate that the effect of treatment would be permanent. This finding, in and of itself, would not exclude the possibility that the use of oral contraceptives could have a temporary protective effect on disease in women during use. However, it was found in a very large study that the incidence rates for MS in current users of oral contraceptives were not decreased as compared to never-users.[29] This latter observation would suggest that the estrogens in oral contraceptives are not of the adequate type or dose to reduce the immunopathogenesis of MS during use. Therefore, it is likely that a sustained level of a sufficient dose of an estrogen, creating an estrogen profile similar to that of pregnancy, would be necessary to reduce disease activity in MS.

REFERENCES

1. Bebo Jr. BF, Vandenbark AA, and Offner H: Male SJL mice do not relapse after induction of EAE with PLP 139–151. *Journal of Neuroscience Research* 1996;45:680.

2. Palaszynski KM, Loo KK, Ashouri JF, Liu H, and Voskuhl RR: Androgens are protective in experimental autoimmune encephalomyelitis: implications for multiple sclerosis. J N*euroimmunol* 2004;146:144.

3. Wang C, Alexander G, Berman N, Salehian B, Davidson T, McDonald V, Steiner B, Hull L, Callegari C, and Swerdloff RS: Testosterone replacement therapy improves mood in hypogonadal men—a clinical research center study. *Journal of Clinical Endocrinology and Metabolism* 1996;81:3578.

4. Wang C, and Swerdloff RS: Androgen replacement therapy. A*nnals of Medicine* 1997;29:365.

5. Foster SC, Daniels C, Bourdette DN, and Bebo Jr. BF: Dysregulation of the hypothalamic-pituitary-gonadal axis in experimental autoimmune encephalomyelitis and multiple sclerosis. J N*euroimmunol* 2003;140:78.

6. Wei T, and Lightman SL: The neuroendocrine axis in patients with multiple sclerosis. B*rain* 1997;120:1067.

7. Pozzilli C, Tomassini V, Marinelli F, Paolillo A, Gasperini C, and Bastianello S: 'Gender gap' in multiple sclerosis: magnetic resonance imaging evidence. E*ur J Neurol* 2003;10:95.

8. Bansil S, Lee HJ, Jindal S, Holtz CR, and Cook SD: Correlation between sex hormones and magnetic resonance imaging lesions in multiple sclerosis. A*cta Neurologica Scandinavica* 1999;99:91.

9. Pozzilli C, Falaschi P, Mainero C, Martocchia A, D'Urso R, Proietti A, Frontoni M, Bastianello S, and Filipp M: MRI in multiple sclerosis during the menstrual cycle: relationship with sex hormone patterns. N*eurology* 1999;53:622.

10. Tomassini V, Giugni E, Mainero C, Onesti E, Giuliani S, Paolillo A, Bastianello S, Salvetti M, and Pozzilli C: Relationship between sex hormones and MRI activity in relapsing-remmitting multiple sclerosis. N*eurology* 2001;56:A254.

11. Smith R, and Studd JW: A pilot study of the effect upon multiple sclerosis of the menopause, hormone replacement therapy and the menstrual cycle. *Journal of the Royal Society of Medicine* 1992;85:612.

12. Abramsky O: Pregnancy and multiple sclerosis. A*nnals of Neurology* 1994;36 Suppl:S38.

13. Birk K, Smeltzer SC, and Rudick R: Pregnancy and multiple sclerosis. S*emin Neurol* 1988;8:205.

14. Birk K, Ford C, Smeltzer S, Ryan D, Miller R, and Rudick RA: The clinical course of multiple sclerosis during pregnancy and the puerperium. A*rch Neurol* 1990;47:738.

15. van Walderveen MA, Tas MW, Barkhof F, Polman CH, Frequin ST, Hommes OR, and Valk J: Magnetic resonance evaluation of disease activity during pregnancy in multiple sclerosis. *Neurology* 1994;44:327.

16. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, and Moreau T: Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group [see comments]. *New England Journal of Medicine* 1998;339:285.

17. Vukusic S, Hutchinson M, Hours M, Moreau T, Cortinovis-Tourniaire P, Adeleine P, Confavreux C, and G [last name?]: The Pregnancy In Multiple Sclerosis. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. *Brain* 2004;127:1353.

18. Damek DM, and Shuster EA: Pregnancy and multiple sclerosis. *Mayo Clinic Proceedings* 1997;72:977.

19. Runmarker B, and Andersen O: Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis [see comments]. *Brain* 1995;118:253.

20. Villard-Mackintosh L, and Vessey MP: Oral contraceptives and reproductive factors in multiple sclerosis incidence. *Contraception* 1993;47:161.

21. Hernan MA, Hohol MJ, Olek MJ, Spiegelman D, and Ascherio A: Oral contraceptives and the incidence of multiple sclerosis. *Neurology* 2000;55:848.

22. Voskuhl R: Sex hormomes and other pregnancy-related factors with therapeutic potential in multiple sclerosis. In *Multiple Sclerosis Therapeutics*, 2003;Vol. 32. D. Cohen, and R. Rudick, eds. Martin Dunitz Ltd., London, p. 535.

23. Follingstad AH: Estriol, the forgotten estrogen? *Jama* 1978;239:29.

24. Head KA: Estriol: safety and efficacy. *Altern Med Rev* 1998;3:101.

25. Taylor M: Unconventional estrogens: estriol, biest, and triest. *Clin Obstet Gynecol* 2001;44:864.

26. Utian WH: The place of oestriol therapy after menopause. *Acta Endocrinologica Supplementum* 1980;233:51.

27. Sicotte NL, Liva SM, Klutch R, Pfeiffer P, Bouvier S, Odesa S, Wu TC, and Voskuhl RR: Treatment of multiple sclerosis with the pregnancy hormone estriol. *Ann Neurol* 2002;52:421.

28. Soldan SS, Retuerto AI, Sicotte NL, and Voskuhl RR: Immune modulation in multiple sclerosis patients treated with the pregnancy hormone estriol. J I*mmunol* 2003;171:6267.

29. Thorogood M, and Hannaford PC: The influence of oral contraceptives on the risk of multiple sclerosis. B*r J Obstet Gynaecol* 1998;105:1296.