NEUROENDOCRINE REGULATION IN MS

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OVERVIEW

There are marked sex differences in the risk of multiple sclerosis (MS), with almost three times more women than men developing the disease. Over the course of the disease, there is evidence of neuroendocrine regulation of both the inflammatory and neurodegenerative mechanisms at play in MS. In the current primer, we will focus mainly on the hypothalamic-pituitary-gonadal axis, with other endocrine pathways (thyroid, adrenal, vitamin D regulation) being briefly mentioned.

GONADAL STEROIDS.

Women.

- Endogenous hormonal exposures:
    - **Menarche**. The age at menarche has been decreasing over the past decades, and downstream events associated with earlier reproductive maturation have been hypothesized as one mechanism explaining an apparent increase in the female:male sex ratio in multiple sclerosis.(1) There is a growing literature about the role of changes at puberty playing a role in the development of MS risk:(2) earlier menarche, a risk factor MS, has been tied with earlier onset of MS symptoms as well in some studies. Mechanistically, it is possible that this association is causal, through an effect of cycling gonadal hormones on immune regulation, inflammatory events, and ongoing neuronal development and susceptibility. This is supported by a recent report of increasing relapses as adolescent girls transition through puberty.(3)

      However, it is also possible that earlier menarche reflects an earlier adipose, pro-inflammatory childhood and adolescent environment. An association between adolescent obesity and MS risk, first reported in the Nurses' Health Study, has been replicated for both adult-onset and childhood-onset MS;(4) and with earlier age of MS onset. The role for adiposity-related inflammatory mechanisms is supported by a striking interaction between adolescent obesity and HLA risk genes in predicting adult onset MS.(5)

    - **Childbearing.** *Pregnancy*. It is well established that there is a decreased risk of relapses during pregnancy. This is followed by an increased relapse rate postpartum: up to one third of women may relapse in the first three months postpartum, and relapses may worsen long-term disability. This fluctuation in relapse risk, which is overall consistent with the immunotolerant state of pregnancy,(6, 7) appears to mirror fluctuations in the levels of the pregnancy estrogen estriol. Over the whole pre- to post-pregnancy period, the relapse risk appears to be similar to the non-pregnant state. Women with higher risk of postpartum relapse may have experienced high relapse rate in the year prior to pregnancy, and have a higher level of disability at the time of conception. (8)

      *Breastfeeding***.** While there is wide variability in the intensity and duration of breastfeeding across cultures and individuals, overall it appears that exclusive breastfeeding (breastmilk not supplemented by any formula or other sources of nutrition) has a protective effect against post-partum relapses, while non-exclusive breastfeeding may not.(9-11) In a meta-analysis of existing small studies, the risk of postpartum relapses was halved with any breastfeeding.(12) An important confounder is disease activity, which can alter a patient's decision to breastfeed or restart disease-modifying treatment immediately postpartum.

      *Parity***.** Delayed childbearing and nulliparity have both been associated with increased risk of MS. Experiencing a pregnancy after MS onset reportedly has either no adverse effects on maternal MS

progression and disability,(13-15) or a beneficial effect.(16-22) Confounders which have been overlooked in some studies include reverse causation, whereby women with more severe disease are less likely to have children,(16) and older age at MS onset.

- **Menopause.** A majority of women develop MS prior to the menopausal transition. Not enough is known about whether menopausal factors influence a patient's MS symptoms, disease course, or quality of life. The median age at natural menopause, about 51.5 years, seems to be in line with age at natural menopause in western societies, suggesting that MS does not influence the timing of menopause.(23) While not enough is known, there may be a slight worsening of MS course as levels of ovarian hormones decline,(23, 24) presumably due to the effects of estrogen loss on neurodegeneration. There are very limited objective data on the effect of hormone replacement therapies on MS course. (25)

Exogenous hormonal exposures:

- **Oral contraceptives** have, in observational studies, been reported to have either protective, neutral or negative effects on MS risk. Additionally, oral contraceptives have been reported to have variable effects on MS course: protective effects against EDSS progression in relapsing-onset MS, but opposite effects in primary progressive MS. In a recent observational cohort, OC use (current, prior, never) was not associated with relapse rate in women with early-onset MS starting a platform injectable DMT. (26) These studies may be confounded by the effect of OCs on delaying childbearing and the fact that medication composition (estrogen and/or progestogen; dosing) may have varied between the relevant study epochs, with possibly differing effects on inflammatory activity. (8) Mechanistically, the relative stability in hormonal levels afforded by an OC might temper fluctuations in the inflammatory cascade that leads to new lesions and clinical relapses; as preliminary support for this, MS-related symptoms reportedly increased during the "pill-free" week in women taking combined estrogen/progesterone OC.(27)

  In a recent randomized trial in relapsing MS, women receiving IFN-β-1a subcutaneously plus *ethinylestradiol 40 µg and desogestrel 125 µg* had fewer active lesions on brain MRI at week 96 than women receiving only IFN ($p = 0.04$); and a greater proportion of participants had no gadolinium-enhancing lesions ($p = 0.03$).(28) A recent trial of *estriol* (an estrogen markedly elevated during pregnancy, and that at lower doses has been used as HT in Europe and Asia) for 24 months as an add-on to GA suggested a modest effect on relapse rate.(29)

  Taken together, these observational and interventional studies suggest that exogenous estrogens (+/- progestogens), when administered for contraceptive use, are not *harmful* to women with MS of childbearing age, and may even be protective against relapses.

- **Progesterone.** The Prevention of Post-Partum Relapses with Progestin and Estradiol in Multiple Sclerosis (POPART'MUS) trial, involving high doses of progestin, in combination with endometrial-protective doses of estradiol, finds these hormones did not provide any protective effect from relapses.

- **Assisted Reproductive Technologies.** several small studies have reported an increased risk of relapses following ART.(30) This elevated relapse risk was reportedly more prominent after unsuccessful cycles, and after ovulation stimulation with gonadotropin-releasing hormone (GnRH) agonists rather than antagonists. There was not consistent assessment of confounding from DMT interruption or emotional stressors. Given these reports, MS and fertility providers should interface prior to ART cycles.

MEN.

Of particular interest to many men with MS are reports of hypogonadism either preceding the onset of MS or early in the MS disease course. It is known that androgen levels decline with chronic illnesses. (31) It could be predicted that, as for men in the general population, testosterone supplementation could result in improved libido, muscle mass and energy i.e. physical quality of life (QOL). A very small pilot trial reported beneficial effects of testosterone gel on brain atrophy (32), although larger studies are needed to assess the relative balance of benefits and risks (including cardiovascular and prostate) of testosterone therapy in men with MS.

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