

GENDER-SPECIFIC CARE CONSIDERATIONS IN MULTIPLE SCLEROSIS

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Education Session Objectives: Participants should be able to identify 1) significant differences between neurological disease expression in men and women 2) potential complications with and ways to support choices in contraception, fertility and reproductive aging care (menopause or andropause).

Part 1: Multiple sclerosis

Introduction:

Multiple sclerosis is an autoimmune demyelinating disease of the central nervous system. Like many autoimmune diseases there is sex dimorphism in both disease risk and phenotype.

- In most countries the sex ratio of MS risk is ~3:1 females to males
- However the incident MS sex ratio in pre-pubertal children and adults over age 50 is closer to 1:1.¹⁻³
- While women are more likely to develop MS, men often exhibit earlier or faster disability accumulation.⁴⁻⁶
- Sex dimorphism in phenotype, however, diminishes after the age of fifty.
- Thus, the biology of female fertility may be driving dimorphism

Important biological events in men and women should be considered in clinical management choices and supporting wellness in MS patients.

Puberty:

The increased risk of MS among females manifests only after puberty, suggesting a role for pubertal development in MS risk.³ The influence of puberty on disease course is less clear, but in a small pilot study menarche in girls was associated with a spike in relapse risk.⁷ In girls with pre-pubertal onset often managed on injectable therapies, signs of pubertal onset may warrant increased vigilance for new disease activity.

Menarche onset in girls also warrants consideration of pregnancy and birth control in patient counseling. It is important to let families know that some MS medications are not compatible with pregnancy and that if they are used in adolescents birth control should be considered.

The effect of puberty on disease course in boys is not known but earlier sexual maturity has been found to be associated with earlier onset of MS.⁸

Fertility, sexual function, and contraception in women:

There has been no evidence to suggest that having MS impairs female fertility.⁹ Some medications like cyclophosphamide can impact fertility, but MS itself has not been shown to decrease pregnancy success.

This being said depressed mood, pain or impaired sexual function can affect family choices and should be addressed as appropriate. Multiple studies indicate that approximately 70-85% of women with MS experience sexual dysfunction and that they experience more dysfunction than women with other chronic illnesses or healthy women.¹⁰⁻¹²

Sexual dysfunction in women with MS can be secondary to psychological factors or physiological factors. Regarding the former, potential depression, anxiety, stress or body image concerns can contribute to dysfunction. Pharmacological treatments or therapy with a mental health provider should be considered. A trained therapist in sexual health may also be of significant help to the patient and her partner. Care should be taken in prescribing anti-depressants as some interfere with sexual function.

Physiological changes related to MS can impair sexual function in women.^{12, 13} Changes or loss in sensation can impact arousal. Heightened sensations or spasms can create discomfort associated with sexual activity. Vaginal dryness can contribute to painful intercourse. Medication can be used to control neuropathic pain or decrease uncomfortable muscle spasms that may occur. Vaginal lubricants can be used to decrease painful intercourse. Pelvic floor muscle training has also been shown to improve sexual dysfunction in women with MS.¹⁴

Exercise and overall improved wellness approaches including healthy diet and stress reduction programs may have significant impact on sexual function as well.

No form of birth control has been *consistently* shown to negatively or positively affect MS disease course. Thus, generally speaking, contraception methods can be chosen based on best fit for the patient with consultation from a gynecologist. One exception is that for medications with pregnancy-associated risks, the more reliable forms of birth control should be strongly considered.

Fertility, contraception and sexual function in men:

There is no data to suggest that men with MS have impaired fertility. However, up to 90% of men with MS report sexual dysfunction^{11, 15}, which can affect relationships and family planning.

As in women, both psychological and physiological factors can contribute to a change in sexual function. Mood changes or anxiety, stress and body image related concerns should be addressed. Referrals to mental health providers or sex therapist should be considered. Medications should be reviewed to look for agents that can have sexual function side effects.

Physiological causes of dysfunction in men include decreased sensation, difficulty in achieving or maintaining an erection, and incomplete or lack of ejaculation.¹⁵ Treatment options include erectile dysfunction pharmaceuticals such as sildenafil¹⁶, tadalafil¹⁷, or vardenafil or injectable medications like papaverin, phentolamine, or alprastodil^{15, 18} to increase local blood flow and promote erection. Penile devices are also available to mechanically address dysfunction. These include patient controlled inflatable devices and surgically implanted devices. Consultation with a urologist is recommended.

If inability to ejaculate prevents starting a family, consultation with a fertility center is also recommended to pursue treatments such as insemination. Testing for abnormal male hormone levels can also be pursued as appropriate, especially as testosterone levels may be low in patients with MS.

Regarding contraception for males, use of teriflunomide requires that males and their partners take precautions against pregnancy, as there is some concern for fetal risk with paternal exposure to the medication. No known adverse pregnancy events have been reported yet associated with male exposure to this medication but based on mechanism of action of the drug and similar pharmaceuticals caution is strongly advised.

Pregnancy:

As pregnancy related concerns in MS are covered in great detail in another annual AAN course, we will only briefly review the highlights here.

- Pregnancy is associated with a decrease in relapse activity with the greatest protection in the third trimester.¹⁹
- Injectable medications are generally thought to be safer at least for conception if not for the full duration of pregnancy.^{20, 21} Conclusions regarding safety are driven largely by registry data as well as mechanism of action and animal data.

- None of the MS oral medications can be onboard during conception or during pregnancy or breastfeeding.²⁰ Wash out periods before conception vary for the three oral agents and careful communication should occur among patient, neurologist and obstetrician/fertility provider about timing of ceasing contraception.²¹
- If needed for particular patients, natalizumab use in pregnancy can be considered in careful consultation with the patient, but should if possible be stopped by week 26-28 to avoid hematological complication in the newborn.²²
- There is a spike in relapse risk in the immediate post-partum period, although only approximately 25% of women experience post-partum relapses.¹⁹
- Exclusive breastfeeding may at least partially reduce the risk of post-partum relapses.⁹

Aging with MS:

The biological changes of normal female and male aging can interact with the symptoms of multiple sclerosis leading to additional considerations for improving patient quality of life in this age group.

Perimenopause in women

Long before the last menstrual cycle, women may experience up to a decade of symptoms from ovarian function decline. Most typically these symptoms begin in the mid-forties but may start earlier or later. Generally, women tend to experience menopausal symptoms when their mothers did.²³ Unfortunately, the vasomotor symptoms (eg. "hot flashes") and bladder function changes common to the perimenopause period can exacerbate MS symptoms.²⁴ Working together with a women's health specialist and urologist and consideration of pelvic floor therapy or biofeedback can make significant impact on symptoms. Use of estrogen medications or estrogen mimic agents to help alleviate symptoms requires careful consultation with the patient and consideration of her personal and family history of cancer.

The mean age of onset of secondary progressive MS (SPMS) is 45 years of age²⁵ and while the potential connection of peri-menopause with onset of SPMS is not yet firmly established, there is preliminary evidence that a biomarker of ovarian function is associated with disability accumulation in women with MS.²⁶ In any case, this is a time for careful observation and detailed examinations to determine if there are phenotypic changes in disease expression that should be better addressed with changes in management.

This is also an excellent time period to re-emphasize the importance of exercise and overall wellness including healthy diet and stress reduction. These can help reduce perimenopausal symptoms as well as help to maintain physical function.

Post-menopausal period

After menopause female risk for many diseases changes and this is an optimum time to ensure that the patient has a primary care provider outside the MS clinic and that she is obtaining age-appropriate screening.

Andropause in men

After the age of 30 in men, testosterone declines by approximately 1% per year. For some men there may be greater dips in levels. Hypogonadism can occur with significantly lowered levels and create symptoms of fatigue, decreased sex drive, erectile dysfunction, difficulty concentrating, hot flashes, and decrease in muscle or bone mass.²⁷ In men with MS suffering from the above symptoms, testosterone levels should be checked. Low testosterone levels have been associated with increased risk of MS and with more severe phenotype in both human and animal studies.^{28, 29} While the causal relationship between MS and testosterone is still under investigation, testosterone replacement may help with chronic symptoms and quality of life for men with MS.

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