HHS Public Access

Author manuscript

Mov Disord. Author manuscript; available in PMC 2015 June 01.

Published in final edited form as:

Mov Disord. 2014 June ; 29(7): 845–848. doi:10.1002/mds.25891.

The Complexities of Hormonal Influences and Risk of Parkinson's Disease

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Women have a lower incidence of Parkinson's disease (PD) than men.[1] Once diagnosed, women may have slower progression of disease[2] and different clinical features. Women with PD appear to have more dyskinesias and less levodopa requirements, even when adjusted for body weight.[2–4] Sex-based differences in disease may be attributed to hormonal differences as well as differences in environmental exposures (reviewed by Savica et al.[5]), relative genetic load,[6] gene–environment interactions,[7] and possibly practice-related treatment differences.[8]

Over the past several decades a major drive has been conducted to understand the role of exogenous and endogenous sex hormones as mediators for sex-based differences in the prevalence, presentation, and course of a variety of diseases (orwh.od.nih.gov). Experiments in vitro and in animal models[3–7] of Parkinson's disease and other degenerative disorders have focused on the neuroprotective properties of estrogen as a biologically plausible explanation for the relatively milder phenotype of female PD. They have suggested anti-inflammatory,[9–11] anti-apoptotic,[12] and anti-oxidative effects.[13] To further establish causal inference, these basic science studies have been complemented by a number of observational studies evaluating the relationship between life events affecting womens' endogenous sex hormone balance, intake of exogenous sex hormones, and PD risk.

Although no hormonal factors have been universally associated with PD risk across all observational studies, one of the more consistent observations has been an association between early menopause, whether natural or surgical, and increased risk of PD.[14–16] Also, oophorectomy before menopause was shown to increase risk of parkinsonism by 68%.[16] Postmenopausal hormone therapy (HT) has been associated with reduced PD risk in several studies,[14,17] consistent with the prevailing theory of a protective effect of estrogens. However, other studies have failed to find associations,[18,19] and a subset have even observed associations in the opposite direction.[20] Some of the divergent findings between studies may be attributed to the possibility of differential effects of HT, depending on when it is administered relative to a woman's age, type of menopause (natural or surgical), and

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

stage of menopause, such that women with early menopause administered HT at a young age are more likely to demonstrate neuroprotective benefits, whereas late postmenopausal HT may even be deleterious. The positive effect of HT when instituted around the time of menopause is termed the timing hypothesis, and it was first described in the context of a lack of cardiovascular harm from HT when started close to menopause in the Women's Health Initiative Study.[21,22] An allied concept, the critical window hypothesis, which states that estrogen therapy early in menopause is beneficial for the brain but lacks effect or may be deleterious later postmenopause has been applied to models for cognitive decline and Parkinson's disease.[16,23–26]

Women with PD who are approaching or are in menopause frequently inquire about the role of exogenous hormones as a symptomatic or disease-modifying agent, yet because of the conflicting data, counsel is unclear. Increasingly, as more highly at-risk groups, such as carriers of *LRRK2* mutations, are defined, a growing cohort of at-risk women are also seeking advice. They question whether modification of hormonal status, by hormone therapy, oral contraceptives, or choosing not to have oophorectomy or hysterectomy, may decrease risk of developing PD. In this issue of *Movement* Disorders, Liu et al. address these issues.[27]

Liu et al. examine associations between PD and a number of factors related to reproductive history and hormone use, including age at menarche, live births, menopause, oral contraceptive use, postmenopausal HT type, duration, and recency. They evaluated data from the National Institutes of Health American Association of Retired Persons (NIH-AARP) Diet and Health study, which ascertained these exposures between 1995 and 1997 and diagnosis of PD between 2004 and 2006—both by self-report. Over 100,000 women participated in both exposure and outcome surveys. Diagnosis was confirmed by medical record review or by confirmation from the treating neurologist, resulting in 410 cases of PD. Contrary to prevailing belief, neither surgical nor natural menopause, nor age at onset of either type of menopause, was associated with increased PD risk. Only the subgroups of early hysterectomy (<40 years old) without oophorectomy (odds ratio [OR] 1.45) or hysterectomy with bilateral oophorectomy (OR 3.34) were associated with a significantly higher risk of PD when compared with women who underwent natural menopause at ages 50 to 54.

The investigators found a significantly reduced PD risk with long-term oral contraceptive use (OR 0.62 for more than 10 years of use compared with those who never took oral contraceptives). Assessing postmenopausal factors, they report an increased PD risk (OR 1.52) with current HT of less than 5 years' duration compared with no HT, which became lower in magnitude and not significant when restricted to cases diagnosed after 2000 (i.e., restricted to cases with onset of PD more than 3–4 years after "current" HT was reported).

Few findings of Liu et al. help to support the notion that estrogens protect women from PD. Increased risk with bilateral oophorectomy, presumably associated with earlier menopause and falling estrogen levels, is consistent with findings of others.[14–16] Reduced risk with long-term oral contraceptive use is novel, as previous studies have either not shown an association between oral contraceptive use and PD[17,19,20,28] or have suggested an increased

risk,[29] but this observation is consistent with a prevailing theory of estrogen's protective effect. Other findings are more difficult to explain within the context of a model that posits that estrogen protects against the development and manifestations of PD. For example, the finding of an association between PD risk and early hysterectomy without oophorectomy might appear puzzling, because hysterectomy alone is not known to cause a drop in endogenous hormone levels. However, there may be at least a transient decrease in ovarian reserve and hormone production associated with hysterectomy without oophorectomy.[16,30]

Conversely, the investigators found no association with other markers of estrogen exposure that have been demonstrated in prior reports, including age at menarche, age at natural or surgical menopause, or duration of estrogen-containing HT. The absence of these associations led the authors to conclude that little support exists for an important role of estrogen as a mitigator of risk for PD. The beneficial effect of oral contraceptive use could suggest that part of a hormone-mediated effect could be attributed to progesterone rather than estrogen.

Moreover, their finding of an increased risk of PD with short duration (but not longer) current HT is difficult to integrate with our theories of the biological effects of hormones or with ideas regarding the long prodromal period of PD. Perhaps the more intense general medical scrutiny that patients are under during the period of several years leading up to the diagnosis of PD leads to a higher likelihood of initiation of HT.

Although several limitations to the study should be noted, including the imprecise self-report of exposures, retrospective ascertainment of history of all reproductive factors and hormone intake, as well as the lack of information on timing of HT relative to onset of menopause or relative to diagnosis of PD, the authors provide a generally well-conducted study and the largest sample studied to date with which to address the role of hormones in PD.

Given the inconsistent findings of Liu et al., one could argue that this suggests a lack of effect of reproductive factors. Reconciling the discrepancies between studies to date is difficult. These may reflect associations of small magnitude being obscured by noise inherent in exposure and life-history recall, inaccuracies of case identification, and unmeasured confounders. Even if prospective assessment is possible, additional complexities of measuring life-long estrogen exposure exist. Studying the effects of estrogen exposure is made complicated by many factors, including variable sources (endogenous, exogenous), multiple formulations of contraceptives and hormone therapies, timing (from adolescence to the postmenopausal period, through pregnancies and menstrual cycles), and environmental influences (such as caffeine and smoking). Studies have demonstrated modification of the association between caffeine intake and PD by postmenopausal hormone use (or vice versa),[29] and smoking itself is associated with earlier age at menopause.[31] In addition, pesticides may increase PD risk by blocking the effects of estrogens.[32] These may be only the tip of the iceberg of interactions between environmental influences and exogenous or endogenous estrogen, and it is unlikely that observational studies will be definitive on this subject. Finally, estrogen is not the only sex steroid hormone, and progesterone, testosterone, anti-Müllerian hormones, or others also may be contributing to differential effects in women.

Prospective measurement of reproductive factors, particularly those more prone to recall bias such as age at menarche, menopause, and hormone use, could help mitigate this problem, but it will require unique prospective cohort designs. Despite this being one the largest studies to date on this topic, the confidence intervals are still broad and may have missed small to moderate-sized associations. This underscores the critical role that large prospective cohorts would have to play to advance our understanding of risk factors for less common and later-onset diseases. Many of the prospective studies to date, such as the Nurses Health Study, the Women's Health Initiative, and the NIH–AARP Diet Study described herein, had specific goals that initially were not related to examining the relationship between endogenous and exogenous hormones and Parkinson's disease. Furthermore, whereas the quantification of hormonal events is greater in the Women's Health Initiative, for example, than the NIH-AARP study, with the definition of age of menopause more precise, determination of PD status is less rigorous,[33] leading to potential overestimates in cases. Also, most of the women in the Women's Health Initiative were perimenopausal or postmenopausal at the time of study onset. Longitudinal mid-life studies incorporating more detailed hormonal assessments, including serum hormone measurements, such as the Study of Womens' Health Across the Nation, may provide the data required to better address questions of estrogen effects in PD. To be most useful for studying PD risk, exposure measurements should, if possible, include environmental factors that may be relevant for PD, and surveillance for incident parkinsonism should be integrated early in the studies. However, to provide a sufficient number of incident cases for this relatively uncommon, and primarily late-onset disorder, multiple studies likely will need to be pooled.

At present, for those women who consider themselves at higher risk of PD because of a family history, or those who harbor a mutation in a PD-causing gene, or have PD and are in transition to menopause, no definitive answers regarding potential disease-modifying effects of hormonal therapy or hysterectomy and oophorectomy can be given at this time. Hopefully, large prospective initiatives such as those mentioned can eventually allow us to provide some definitive guidance.

Acknowledgments

Funding agencies: This study was supported by grants from a New Investigator award from the Canadian institutes of Health Research to Connie Marras and a National Institutes of Health (NIH) grant K02-NS073836 to Rachel Saunders-Pullman.

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