Reproductive life milestones in women with Parkinson's disease

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Summary

Reproductive life milestones were studied in 150 unselected women with idiopathic Parkinson's disease (PD) and in 300 postmenopausal healthy women (PM). Duration of reproductive life was found to be similar in the two groups. The women with PD reported significantly more premenstrual symptoms, fewer deliveries and abortions, and less use of contraception. Time and mode of menopause onset were similar in PD and PM, but the PD women reported significantly more hot flushes, less insomnia, depression, urinary incontinence and dyspareunia, and less recourse to hormone replacement therapy than the PM women. Women diagnosed with PD before the menopause reported more premenstrual symptoms and contraceptive use compared with those with postmenopausal PD onset, as well as a premenstrual worsening of PD symptoms in more than 50% of cases. Our data indicate poor adaptation of neuronal pathways to the hormonal fluctuations of reproductive life in women with PD, supporting the existence of a qualitative relationship between PD and reproductive events.

KEY WORDS: contraception, hormone replacement therapy, menopause, menstruation, parity, Parkinson's disease.

Introduction

Parkinson's disease (PD) is more frequent in men than in women (1), and its clinical profile also displays gender differences, with men showing more severe motor impairment and behavioural problems, and women more marked dyskinesia and depression (2). Accordingly, a role of gonadal hormones in PD may be suggested, also taking into account the positive role of oestrogens on symptom severity (3,4) and on response to levodopa (5) and possibly other drugs (6), and the negative effect of the premenstrual phase on symptom severity and response to therapy (7), even in the absence of a significant relationship between PD symptoms and premenstrual hormone levels (8). On the other hand, there is no consensus regarding the potential role of oestrogens on the course of PD during the menopause. Indeed, on the one hand, there exists evidence of PD improvement (9) during the hypo-oestrogenic state and, on the other, findings suggesting that conditions causing an early reduction in endogenous oestrogens may increase the risk of PD (10), while a short placebo-controlled, randomized, double-blind trial was unable to demonstrate any significant effect of oestradiol on PD symptoms in postmenopausal women (11). Indeed, oestrogens, acting via both genomic and non genomic mechanisms (12), have widespread effects (not only gender-related) in the brain throughout the life span, but their role on the basal ganglia is still to be elucidated.

The few studies that have considered a possible gender effect in PD women set out to explore the anterior pituitary function in relation to the safety of drug treatments (13) or concerned a small number of postmenopausal women, in whom altered neuroendocrine regulation of luteinizing hormone was possibly attributable to reduced activity of the endogenous opioid system (14).

In this evaluation of reproductive life milestones in PD women, we considered pre- vs postmenopausal onset of PD symptoms, in order to verify whether oestrogenic state may be relevant to the clinical expression of the disease. A group of postmenopausal women (PM) was also recruited to enable us to look for possible differences, between our patients and healthy controls, in characteristics specifically related to fertile life span.

Materials and methods

Subjects

One hundred and fifty women with idiopathic PD, presenting mild to moderate motor symptoms and without clinically detectable cognitive decline, attending the Parkinson's disease and movement disorders centres of the IRCSS C. Mondino Institute of Neurology in Pavia and the Ospedale di Circolo – Fondazione Macchi in Varese, were consecutively recruited for the study, in which all consented to participate.
Three hundred postmenopausal women (absence of menstrual bleeding for at least 6 months and FSH levels higher than 30 mUI/L) observed at the Department of Obstetrics and Gynaecology at the IRCCS San Matteo Hospital in Pavia, and showing no evidence of either central or peripheral nervous system abnormalities, were chosen as the control group.

Study Design

The investigation was conducted using an "ad hoc" questionnaire divided into 3 sections. The first section, completed upon entering the study, collected demographic data and included a detailed history of PD (age at onset, duration and phase of disease [stable or fluctuating], UPDRS and H&Y [in on and off], drug therapy, etc.). The second section, designed by a gynaecologist (REN), investigated reproductive life milestones: menstrual cycle (age at menarche, length of menstrual cycles [eumenorrhoea: 26-32 days; oligomenorrhoea: more than 32 days; polymenorrhoea: shorter than 26 days], menstrual bleeding [light: no more than 3 days; normal: 3-5 days; heavy: more than 5 days], dysmenorrhoea [presence of moderate or severe pain during menstrual bleeding], premenstrual syndrome [presence of psychological symptoms such as depression, anxiety, irritability, etc. and/or physical symptoms such as bloating, mastodynia, water retention, etc. prior to expected menstruation]), pregnancy and childbirth (parity, number of spontaneous and voluntary abortions, breastfeeding history), oral contraceptive use, menopause (age, mode, premenopausal menstrual irregularities, presence of climacteric symptoms such as hot flushes, depression, irritability, anxiety, insomnia, vaginal dryness, urinary incontinence, dyspareunia etc., use of hormone replacement therapy), gynaecological diseases (fibroids, ovarian cysts, uterine polyps, endometriosis, cancer, etc.).
The third section investigated the relationship between the onset of neurological symptoms and the time of the menopause, the course of PD throughout menopause and under hormonal treatments and the possible worsening of symptoms around the menstrual period (if PD onset was before the menopause).
Once the subjects had given their informed consent to the treatment of their data for scientific purposes, the questionnaire was administered. The clinical data were gathered by neurologists and gynaecologists skilled in PD and in the menopause respectively, after which the rest of the questionnaire was administered by trained medical interviewers. Interviews were performed face to face both with the PD patients and with the PM controls. All relevant clinical data were confirmed by hospital records. The PM women skipped parts of section 1 and all of section 3. The data were treated to maintain anonymity. The protocol was approved by the local ethics committees.

Statistical analysis

The data were collected in a data base (Excel '97, Microsoft) and analyzed using SPSS 10.0 for Windows. Continuous measures were reported as mean values ± standard deviations. For all variables, frequency measures were performed; univariate comparisons between the two groups were conducted using χ^2 test for quantitative variables and ANOVA for continuous values. Given the simply exploratory design of the study, the frequency analysis of the variables and the univariate comparisons were considered adequate and more complex statistical analyses were not applied.

Results

Study samples

Parkinson's disease women. The 150 women with PD had a mean age of 65.5±9.3 years (range: 42-85 years), and a mean education of 7.6±3.4 years. Their age at onset of PD symptoms was 56.8±10.6 years (range: 28-76) and their mean disease duration was 8.7±6.1 years, ranging from 1 to 35 years. One hundred and forty-one women had been receiving specific therapy for 8.7 years (range: 1 month to 33 years). Fifty-six patients (37.3%) were receiving only one drug, levodopa or a dopamine agonist, while 70 (46.7%) were on two drugs, usually levodopa associated with a dopamine agonist (pramipexole, pergolide, cabergoline, ropinirole, bromocriptine, lisuride) or COMT inhibitor, 22 (14.7%) were on three drugs (levodopa plus dopamine agonist plus selegiline or COMT inhibitor), and 2 (1.3%) were receiving four drugs. The mean dose of levodopa was 547.34±305.86 mg/day (range:100-2500 mg/day). Fifty-seven women (38%) were in the stable phase of PD, with a median H&Y stage of 2 (range 1-3) and mean UPDRS score of 18.28±1.8. Ninety-three subjects (62%) were fluctuating, with median H&Y stage of 2.5 (range 1-3) in the on phase and 3.5 (range 1.5-5) in the off phase, associated with UPDRS mean scores of 27.06±2.37 and 44.33±3.51 respectively.

Postmenopausal women. The 300 PM women had a mean age of 63.5±10.1 (range 44-80) and a mean education of 7.9±3.1 years.

Reproductive characteristics

The reproductive milestones in the PD and PM women are detailed in Table I. Menarche in the PD women occurred significantly later than in the PM women ($p<0.0001$), but within the normal age range. Compared with the controls, the PD women were more affected by premenstrual symptoms ($p<0.0001$), while they reported less use of oral contraceptives ($p<0.0001$), they also recorded significantly fewer deliveries ($p=0.006$) and, as indicated in figure 1, were more likely to be childless. They also recorded fewer spontaneous ($p=0.002$) and voluntary ($p=0.028$) abortions than the healthy women.

Menopause occurred at the same age in the PD and PM women and the reproductive life span was similar in the two groups, as were time and mode of menopause onset. As regards menopausal symptoms, hot flushes were more common among PD women (p=0.001), while depression, insomnia, urinary incontinence and dyspareunia were more frequently recalled by the PM women (p=0.001) (Table I). The percentage of women taking hormone replacement therapy (HRT) was significantly lower among the PD patients (p=0.001).

Onset of PD symptoms and reproductive life span

Thirty-eight of the PD sufferers (25.3%) were diagnosed during their fertile life ("younger PD women"), while in 112 (74.7%) onset of PD occurred after the menopause ("older PD women"). Naturally, the mean age at PD diagnosis was lower (43.0±6.2 vs 61.5±7.1 years; p<0.001) and the mean PD duration greater (12.8±7.4 vs 7.4±4.9 years; p<0.01) in the "younger" vs the "older PD women".
The reproductive characteristics of the two subgroups of PD patients (pre- vs postmenopausal onset of PD symptoms) are shown in Table II (see over). In the group of women diagnosed during fertile life, dysmenorrhoea and PMS were significantly more frequent (p=0.001), as was use of oral contraception (p=0.001). Breastfeeding was reported significantly less frequently by the "older PD women" (p=0.002), while gynaecological diseases were less frequent (p=0.009) in the "younger PD women".

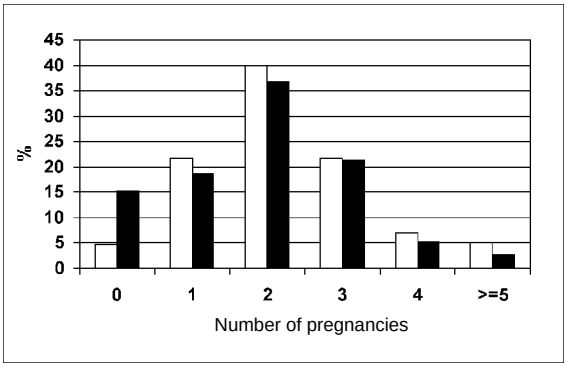

Figure 1 - Frequency distribution of number of pregnancies in PM women (white bars) and PD patients (black bars). $\chi 2$: 16.285, df 5, p=.006.

Table I - Reproductive characteristics of PD patients and PM women.

Study sample (n.)	PM (300)	PD (150)	P value
Menarche			
mean age±SD (range)	12.8±1.4 (9-19)	13.4±1.6 (10-18)	.000
Menstrual cycle			
eumenorrhoea (%)	156 (52.0)	82 (54.7)	ns
dysmenorrhoea (%)	144 (48.0)	68 (45.3)	ns
PMS (%)	97 (33.0)	76 (51.0)	.000
oral contraception (%)	60 (22.2)	14 (9.3)	.000
Pregnancy			
parity (%)	286 (95.3)	127 (84.6)	.006
breastfeeding (%)	178 (62.9)	98 (65.3)	ns
abortions			
spontaneous (%)	89 (30.1)	26 (17.3)	.002
voluntary (%)	25 (8.5)	5 (3.3)	.028
Menopause			
mean age±SD (range)	48.7±4.8 (28-58)	49.1±4.9 (32-59)	ns
natural (%)	222 (74.0)	109 (76.7)	ns
surgical (%)	78 (26.0)	33 (23.3)	ns
HRT (%)	96 (32.0)	34 (23.9)	.001
Climacteric symptoms			
hot flushes (%)	146 (48.7)	98 (65.3)	.001
depression (%)	116 (38.7)	15 (10.0)	.001
irritability (%)	52 (17.3)	19 (12.7)	ns
anxiety (%)	47 (15.7)	20 (13.3)	ns
vaginal dryness (%)	33 (11.0)	16 (10.7)	ns
incontinence (%)	48 (16.0)	7 (4.7)	.001
dyspareunia (%)	42 (14.0)	5 (3.3)	.001
insomnia (%)	83 (27.7)	19 (12.7)	.001
Gynaecological diseases (%)	120 (40.0)	66 (44.0)	ns
Reproductive life span			
mean length±SD (range)	35.9±4.9 (17-46)	35.8±5.1 (18-47)	ns

Table III shows the reproductive characteristics of the 38 PD women diagnosed before the menopause.

Reproductive life span and PD symptoms

A premenstrual worsening of parkinsonism and of response to treatments was found in 52.6% of the 38 "younger PD women", while 43.3% (13 patients) of the 30 who were already postmenopausal at the time of the study reported a worsening of the disease when menses stopped (worsening being defined as the need for increased drug intake or reduced mobility, i.e., requiring assistance, data not shown).
Table IV, considering the entire group of PD women, considers the clinical characteristics of PD patients according to their past use of oral contraception and current use of HRT. The contraceptive users were found to be younger (p=0.0001), to have had more years of education (p=0.036), and a lower age at PD onset (p=0.001) than the non users. Twenty-three of the 142 post-menopausal PD women were taking HRT, and showed no clinical difference vs the untreated PD women. In the patients on HRT, it was interesting to observe that when the treatment induced withdrawal bleeding (10 out of 23), no clinical changes were recorded.

Discussion

This is the first study to investigate the characteristics of reproductive life in women with PD and in healthy subjects. Compared with the healthy women (with whom they were comparable as regards age and geographical and cultural background), the PD women had fewer children and reported fewer spontaneous and voluntary abortions, less use of contraception and more premenstrual symptoms. Other points of interest in the PD women were their low use of HRT and the differences they showed vs the healthy women in their climacteric symptoms: they experienced more hot flushes, but less depression, insomnia and urinary incontinence than the PM women.
Weaknesses of our study are the fact that it is not longitudinal and that it depends upon the recall of the subjects. That said, women are well known to recall their

Table II - Reproductive characteristics of PD patients diagnosed before and after menopause.

Study sample (n.)	PD before (38)	PD after (112)	P value
Menarche			
mean age±SD (range)	13.3±1.8 (11-18)	13.4±1.6 (10-18)	ns
Menstrual cycle			
eumenorrhoea (%)	27 (71.0)	94 (83.9)	ns
dysmenorrhoea (%)	23 (60.5)	45 (40.2)	.001
PMS (%)	24 (63.1)	52 (46.4)	.001
oral contraception (%)	9 (23.7)	5 (4.5)	.001
Pregnancy			
parity (%)	35 (92.1)	93 (83.0)	ns
breastfeeding (%)	31 (81.5)	67 (59.8)	.002
abortions			
spontaneous (%)	4 (10.4)	22 (18.7)	ns
voluntary (%)	2 (5.3)	3 (2.6)	ns
Menopause (n.)	(30)	(112)	
mean age±SD	49.4±4.3	49.0±5.0	ns
natural (%)	28 (93.3)	81 (72.3)	ns
surgical (%)	2 (0.6)	33 (33.3)	ns
premenopausal menstrual irregularities (%)	20 (66.6)	52 (46.5)	ns
HRT (%)	7 (23.3)	16 (14.2)	ns
Climacteric symptoms			
hot flushes (%)	20 (52.6)	78 (69.6)	ns
depression (%)	3 (7.9)	12 (10.7)	ns
irritability (%)	4 (10.5)	15 (13.4)	ns
anxiety (%)	3 (7.9)	17 (15.2)	ns
vaginal dryness (%)	5 (13.2)	11 (9.8)	ns
incontinence (%)	5 (13.2)	2 (1.8)	ns
dyspareunia (%)	4 (10.5)	1 (0.9)	ns
insomnia (%)	9 (23.7)	10 (8.9)	ns
Gynaecological diseases (%)	10/38 (26.3)	56/112 (50.0)	.009
Reproductive life span			
mean length±SD (range)	36.2±5.3	35.6±5.0	ns

reproductive events with considerable accuracy.
When the group of PD women was divided according to disease onset, before or after menopause, no difference in parity was found, although breastfeeding was more frequently reported by the subjects with premenopausal PD onset (the "younger PD women"); this, together with the fact that the "younger PD women" also reported increased use of contraceptives, probably reflects more modern attitudes towards motherhood or a different cultural environment. Alternatively, this in-

Table III - Reproductive characteristics of PD patients diagnosed before menopause according to reproductive status at the time of the study.

Study sample (n.)	Fertile (8)	Menopausal (30)	P value
Menarche			
mean age±SD (range)	13.4±1.9 (11-16)	13.2±1.8 (11-18)	ns
Menstrual cycle			
length			
26-32 days	4 (50.0)	23 (76.7)	ns
<26 or >32 days	4 (50.0)	7 (23.3)	ns
intensity			
normal	4 (50.0)	25 (83.3)	ns
heavy	4 (50.0)	5 (16.7)	ns
duration			
3-5 days	6 (75.0)	24 (80.0)	ns
>5 days	2 (25.0)	6 (20.0)	ns
dysmenorrhoea (%)	6 (75.0)	17 (56.6)	ns
PMS (%)	6 (75.0)	18 (75.0)	ns
oral contraception (%)	2 (25.0)	7 (23.5)	ns
Pregnancy			
parity (%)	5 (62.5)	30 (100.0)	.004
breastfeeding (%)	5 (62.5)	26 (86.6)	ns
abortions			
spontaneous (%)	1 (12.5)	3 (10.0)	ns
voluntary (%)	0 (0.0)	2 (6.6)	ns
Gynaecological diseases	1 (12.5)	9 (30.0)	ns

Table IV - Clinical characteristics of PD patients according to past use of oral contraception and current use of HRT.

Oral contraception	YES (n.=14)	NO (n.=136)	P value
age±SD	55.8±8.9	66.5±8.7	.0001
education (years)	9.4±3.7	7.4±3.3	.036
age at PD onset±SD	47.8±10.9	57.7±10.1	.001
PD length±SD	7.9±4.8	8.8±6.2	ns
UPDRS on±SD	20.1±6.2	24.1±8.8	ns
off±SD	33.9±17.0	34.6±18.7	ns
H&Y on±SD	1.8±0.4	2.1±0.6	ns
off±SD	2.7±1.0	2.8±1.6	ns
HRT	**YES (n.=23)**	**NO (n.=119)**	
age±SD	63.8±7.7	67.1±8.5	ns
education (yrs)	7.8±3.1	7.5±3.4	ns
age at PD onset±SD	55.8±8.0	58.2±10.1	ns
PD length±SD	8.0±4.0	8.8±6.3	ns
UPDRS on±SD	21.4±7.2	24.4±8.9	ns
off±SD	33.8±17.7	35.0±18.9	ns
H&Y on±SD	1.9±0.5	2.2±0.7	ns
off±SD	2.8±1.1	2.9±1.2	ns

Abbreviations: UPDRS=Unified Parkinson's Disease Rating Scale; H&Y=Hoen and Yahr Scale

creased use of contraceptives could also be related to the disease. In fact, it has been found that women with disabilities are more likely to use contraception (15). Negative symptoms related to the menstrual cycle were reported more frequently by the "younger PD women", who gave data similar to those of PM women, while the lower frequency of gynaecological diseases in the "younger" subjects is probably simply due to their greater use of contraception, which can mask ovarian dysfunction.

The observation of reduced parity among PD women is reported here for the first time. It is a finding clearly apparent in the increased level of childlessness among the women with post-menopausal PD onset (the "older PD women"). Meanwhile, the PD women who did have children had a similar number to the PM subjects. That this reduced parity could be a consequence of the PD and of its treatment is thus not the only possible interpretation, another being related to the peculiar behaviour and personality profile that can characterize PD subjects, even premorbidly. Indeed, distinct personality traits, mainly introversion, inflexibility, lack of novelty seeking, have been suggested to be associated with PD (16) and lack of children may reflect peculiar, personal lifestyle choices, even preceding the disease onset (17). Recent data on harm avoidance personality and L-dopa uptake in the caudate nucleus suggest a non dopaminergic pathway for personality traits in PD (18) and that oestrogen metabolizing genes could be involved in the pathogenesis of PD (19), while a study on oestrogen receptor gene polymorphism in PD showed that it does not seem to contribute to PD susceptibility (20), but the same group suggested that exogenous and endogenous oestrogen may modify the risk of PD in women (10).

Other interesting issues are related to the menstrual cycle and concern the perimenstrual symptoms, mainly PMS. PMS was found to be more frequent in the PD than in the PM women and, when PD subjects are evaluated according to their age at disease onset, it is patent that the problem is reported both by the "younger" and the "older PD women", even though it is more prominent in the former, probably due to their more recent experience of the complaints. In healthy women with PMS or in women suffering from menstrual migraine, these symptoms seem to be related to low levels of endorphins (21) and to a reduced neuroendocrine adaptation to cyclic hormonal changes (22). On the other hand, low CSF levels of endorphins have been reported in PD patients, albeit without gender specificity (23). Moreover, in 52.6% of the "younger PD women", premenstrual complaints included a worsening of neurological symptoms and a reduction of pharmacological response. A menstrual cycle effect on PD symptoms has been reported (7). However, it does not seem to be specific to PD, having been found in 52.3% of females with spasmodic torticollis (24), and also in other movement disorders like Tourette syndrome (25), adult-onset focal dystonia (26), as well as in diseases not involving the nervous system (27).

Our data show also that PD women have less recourse to HRT than PM women, although no demographic data or clinical differences emerged between the PD women taking and not taking HRT, in agreement with Kompoliti (8) and Strijks (11); other studies, meanwhile, have shown a slight pro-dopaminergic effect (5) of transdermal 17β-estradiol in post menopausal women, a positive effect of oestrogen use on symptom severity in women with early PD not yet taking L-dopa (3) or with motor fluctuations (4).

Differences were found in the menopausal symptoms recalled by the PD and PM women. The former had more hot flushes than the latter, and less depression, incontinence, dyspareunia and insomnia. Particularly interesting is the fact that PD women recall less depression linked to the climateric period than PM women, while PD subjects, especially women (2), usually score higher rates of depression than healthy controls. However, in our study, which focuses specifically on the climateric period, this finding suggests that the PD women paid more attention to their disease than to their menopause, and were thus better able to tolerate the symptoms associated with their loss of fertility. However, the differences observed in the PD and PM women's perception of climacteric symptoms could also be due to the disease and related treatments, and also to their less frequent use of HRT.

Globally considered, these data could indicate poor adaptation of neuronal pathways to the hormonal fluctuations of reproductive life in women with PD, supporting the existence of a qualitative relationship between PD and reproductive events. Oestrogen could modulate the function of neurotransmitters related to behaviour and movement; further neuroendocrine studies could shed light on the role – also gender-related – of hormone-dependent neural pathways in PD and other movement disorders.

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