Title: My MS and My Menstrual Cycle

Measuring MS symptoms in relation to menstrual cycles: exploring how MS symptoms may be affected at different times during a menstrual cycle in females living with Multiple Sclerosis

Research Team:

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Objective:

To evaluate the severity and timing of MS symptoms with timing of menstrual cycles in women living with MS.

Methods:

Design:

This project is a prospective observational study of females living with MS, tracking MS symptoms in correlation with time of menstrual cycle, measured and correlated via a smartphone app

Inclusion Criteria:

Participants are required to meet the following criteria:

- Females with diagnosed MS by 2024 McDonald Diagnostic criteria [1] (biologically sex-based, any gender as long as not on hormonal gender-enhancing therapy)
- ages 16+, still experiencing menstruation with cycles of 23 to 36 days spacing
- have entered menarche, are experiencing menstrual cycles, and have not yet entered menopause
- participants may utilize hormonal contraceptive methods, such as oral contraceptive methods or hormonal IUDs
- English-speaking
- Willing to provide informed consent, mature minors will provide informed consent, their physician will determine whether their level of maturity is appropriate to participate in the study and complete consent as a mature minor
- Have the ability to complete questionnaires and operate the app

Exclusion Criteria:

People will be excluded as per the following criteria:

- diagnosed with CNS inflammation disorders other than MS such as:
    - NMOSD (Neuromyelitis Optica Spectrum Disorder)
    - MOGAD (Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease)
- male or intersex individuals, given the inclusion criteria of requiring a uterus
- females < 15 years of age
- females who have not started menstruation
- females who have stopped menstruation due to menopause or hysterectomy
- pregnant or postpartum women < 1 year after delivery and/or people who currently breastfeeding
- are unable to provide informed consent, or are not deemed a mature minor to complete consent are unable to complete questionnaires and operate the app

Recruitment:

Via treating neurologists (MS clinic or community-based) and/or nurse practitioners; flyers sent through social media newsletters MS Canada and MS research portal via MS Canada and in clinic rooms/waiting rooms neurologists' practices; mass secure patient messaging via connectcare electronic medical records system

Randomization:

n/a

Intervention:

Eligible patients will download the My Normative app, by scanning a link/QR code. Once registered, electronic consent will be collected through the app. Participants will fill out a baseline series of demographics in addition to a series of patient-reported outcome measures (fatigue, patient perceived level of disability, MS patient symptoms screen, sleep, self-efficacy scale, self-perceived cognition and coping levels, motivation for cognition, and depression and anxiety levels) on the app, as well as enter information re: menstrual cycle tracking/hormone levels as prompted by the app. Participants will then track their menstrual cycles for 6 months with completion of patient reported outcome measures: (1) fatigue – MFIS – 5 item;[2-4] (2) depression & anxiety - HADS;[5] (3) coping (mini-COPE); (4) MFC – motivation for cognition,[6] (5) MSymptoscreen (screen of common MS symptoms)[7] and likert scale from 0 to 7 as to self-perceived cognition levels. This will be done five times per month, as per the different phases of the menstrual cycle. At the end of 6 months, participants will complete an exit scale – with all of the above.

Duration of Study Involvement:

6 months (this has been determined to be optimal in capturing 3 months of menstrual cycles)
This study will be a 2 year study with rolling enrollment

Primary outcomes:

Difference in modified MFIS (fatigue) levels, 5 items during menstruation compared to other times of the menstrual cycle [3, 4, 8-10].

Secondary outcomes:

Qualitative self-reported difference:

- **HADS** (Hospital anxiety and depression scale) – 14 items [5]
- **MNSQ** (Multiple Sclerosis Neuropsychological Screening Questionnaire–Patient Version) - 15 items [10-13]
- **Two Likert scale –** self perceived cognition levels (0 to 7)
- **Coping** – MS specific – Brief COPE Short Version (Mini-Cope) – 12 items (3 different coping styles: active/adaptive, avoidant/maladaptive, and emotional/neutral [14]
- **MFC scale** (motivation for cognition)[6]
- **the SymptoMScreen** - 12 item (walking, hand function/dexterity, spasticity & stiffness, bodily pain, sensory symptoms, bladder control, fatigue, vision, dizziness, cognition function, depression, anxiety), (Green et al Applied Neuropsych 2016)

Sample size:

We plan to recruit a convenience sample over 2 years, with a maximum of 300 participants. There are no substantial prior studies to base the sample size calculation upon.

Hypothesis:

Women with MS experience worsening fatigue, as self-reported by MFIS, during menstruation compared to other times during their menstrual cycles.

1.0 Background and Rationale:

MS most commonly occurs in young adults and persists lifelong.[15, 16] It is associated with a number of physical symptoms such as numbness, weakness, troubles with balance, walking, and vision. However, invisible symptoms of MS are often more debilitating, such as fatigue and cognition (brain fog).[17] MS is more common in women

compared to men, preferentially increasing in women over time as compared to men.[18-21].

There are unique features of multiple sclerosis in women: the course of MS appears to be associated with a number of female-specific features, such as onset in women more after menarche;[22] less inflammatory activity of MS during pregnancy, and increase in the first 3 to 6 months postpartum.[23, 24] Furthermore, exclusive breastfeeding is thought to be slightly neuroprotective in MS.[25-28] Animal model studies suggested an association between female sex hormones in pregnancy and effects on MS inflammation.[29] Therefore, researchers have wondered about the effects of female hormones on the course of MS, with suggested impact upon MRI activity in women living with MS.[30-34] However, it is controversial as to how and whether female hormones impact MS activity, symptoms of MS, progression of MS.[35, 36] Two randomized controlled trials of pregnancy-related sex hormones in women with relapsing remitting MS were negative.[23, 29, 37-39] Despite the lack of definitive association, women with MS have reported fluctuations of MS symptom severity over their menstrual cycles.[40, 41]

A recent prospective study examining MS symptom severity variability at points throughout women's menstrual cycle was published in 2023; participants reported a number of symptoms at different points during their menstrual cycles and there was a suggestion of less fatigue as measured by the MFIS during the perimenstrual period as compared to the luteal period, not felt to be clinically significant, as well as less variability in fatigue reported by women on continuous hormonal oral contraception compared to those who weren't. The authors conclude that more studies are needed to examine the possible relationship between menstruation and MS symptoms.[42]

The My Normative platform app has been used in other populations to track menstrual cycles in relation to various symptoms for women in the general population and other conditions.(mynormative.ca) We hope to examine MS-related symptoms to stages of the menstrual cycle, as measured by the My Normative platform.(mynormative.ca) We hypothesize that MS-related fatigue would be greater in the luteal phase of the cycle as compared to other times of women's menstrual cycles, as measured by the MFIS-5 item.[3] Secondary outcomes will include impact of menstrual cycle stage upon cognition as measured by the likert scale of self-perceived cognitive levels from 1 to 7, various MS symptoms as measured by the SymptoMScreen (walking, hand function/dexterity, spasticity & stiffness, bodily pain, sensory symptoms, bladder control, fatigue, vision, dizziness, cognition function, depression, anxiety),[7] MFC scale (motivation for cognition)[6] and coping (the mini-cope)[14] over a 6 month period with a minimum of 3 months of menstrual cycle tracking. The My Normative platform tracks menstrual cycles in five phases: (1) menstrual phase; (2) follicular phase; (3) ovulation phase; (4) Luteal phase early; (5) luteal phase late

2.0 Proposed Research

Hypothesis:

Women with MS experience worsening of fatigue, as self-reported by MFIS, during menstruation compared to other times during their menstrual cycles.

Design:

Prospective observational self-enrolled study on mobile app.

Setting:

online, app reporting

Subjects:

Females living with MS, who experience menstruation.

Inclusion Criteria:

Participants are required to meet the following criteria:

- Females with diagnosed MS by 2017 McDonald criteria [1] (biologically sex-based, any gender as long as not on hormonal gender-enhancing therapy)
- ages 16+, still experiencing menstruation with cycles of 23 to 36 days spacing
- have entered menarche, are experiencing menstrual cycles, and have not yet entered menopause
- participants may utilize hormonal contraceptive methods, such as oral contraceptive methods or hormonal IUDs
- English-speaking
- Willing to provide informed consent, mature minors will provide informed consent, their physician will determine whether their level of maturity is appropriate to participate in the study and complete consent as a mature minor
- Have the ability to complete questionnaires and operate the app

Exclusion Criteria:

People will be excluded as per the following criteria:

- diagnosed with other CNS inflammation disorders than MS
- male or intersex individuals, given the inclusion criteria of requiring a uterus
- females < 15 years of age
- females who have not started menstruation
- females who have stopped menstruation due to menopause or hysterectomy

- pregnant or postpartum women x 1 year after delivery and/or people who currently breastfeeding
- are unable to provide informed consent
- are unable to complete questionnaires and operate the app

Randomization:

n/a

Questionnaires:

Baseline:

- **PDDS** – single scale (physical disability measure) Patient Determined Disease Steps [43]
- **Full MFIS** – Modified Fatigue Impact Scale (21 point scale) – fatigue [2, 8, 9]
- **HADS** (anxiety & depression) – Hospital Anxiety & Depression Scale (14 items)[5]
- **PHQ9** – Patient Health Questionnaire (depression & anxiety) (9 items)[44, 45]
- **MSNQ** (cognition) (15 item)[11-13]
- **Mini Cope** (coping) (12 item)[46]
- **Pittsburgh sleep quality index** (sleep quality) (24 items)[47]
- **the SymptoMScreen** (12 item) (walking, hand function/dexterity, spasticity & stiffness, bodily pain, sensory symptoms, bladder control, fatigue, vision, dizziness, cognition function, depression, anxiety)[7, 42]
- **MFC scale** (Motivation for Cognition) (10 item)[6]
- **General factors**
    - Demographics (age, race, ethnicity, marital status, level of education, # children, working outside/inside home), BMI, smoking status
    - Years since onset MS (first symptoms) and diagnosis
    - Disease modifying therapies list
    - Medications listt
- **Menstrual cycle information**
    - Length of cycle
- **Type of contraception**
    - Rhythm method
    - No contraception
    - Barrier
        - Condoms
        - Diaphragm
    - IUD (with hormone, without hormone)

- OCP – type – continuous/not continuous

- **5 time points during the menstrual cycle**
  1) Follicular phase, during active menstruation
  2) Follicular phase, no menstruation (leading up to ovulation)
  3) ovulation phase
  4) Luteal phase, first half
  5) Luteal phase, second half (this is the 5-7 days before the next period starts)

Each time point:

- MFIS brief 5 item [3]
- Cognition Likert scale – self perceived cognition levels (0-7)
- SymptoMSScreen 12 item [7]
- Mini-COPE (12 item)[14]
- MFC scale (motivation for cognition) 10 item[6]
- Longer MFIS point scale once per cycle, alternating timing of long scale done at each time point (3 points within cycle) over study duration (6 months) [2, 8, 9]

Study Completion:

- **PDDS** – single scale (physical disability measure) Patient Determined Disease Steps[43]
- **Full MFIS** – modified fatigue Impact Scale (21 point scale) – fatigue[2, 8, 9]
- **HADS** (anxiety & depression) – Hospital Anxiety & Depression Scale – 14 items [5]
- **PHQ9** – patient health questionnaire (depression & anxiety) – 9 items [44, 45]
- **MSNQ** (cognition) 15 item [11-13]
- **Cognition Likert scale –** self-perceived cognition levels (0 – 7)
- **Mini Cope** (coping) (12 item) [46]
- **Pittsburgh sleep quality index** (sleep quality) 24 items [47]
- **the SymptoMScreen** - 12 item (walking, hand function/dexterity, spasticity & stiffness, bodily pain, sensory symptoms, bladder control, fatigue, vision, dizziness, cognition function, depression, anxiety) [7]
- **MFC scale** (motivation for cognition) – 10 item [6]
- Relapses in past 6 months/use of steroids
- Optional - agreement to be contacted to participate in qualitative interview re: use of app

Sample size:

There is not much information or data to calculate sample size. We plan to recruit 300 women living with MS for this study as a convenience/availability sample from the two

MS Clinics at the University of Alberta and University of Calgary (approximately 150 per site).

Taylor et al completed a pilot study, published in 2023, on menstrual cycle and fatigue symptoms in eumenorrheic women living with MS. There was a suggestion of less fatigue in the perimenstrual period compared to the luteal portion of the cycle, and less fluctuation in symptom severity over the cycle for women on continuous hormonal oral contraception. There was a lot of difficulty recruiting for this study with over 200 women contacted and 70 enrolled and 47 providing more than 4 weeks of data for a 6 month period. [42] Despite the challenges faced by these authors, and anticipating a 20% dropout, we plan to try to recruit a maximum of 300 participants over 2 years. There are no substantial prior studies to base the sample size calculation upon.

Analytical Plan:

We will calculate summary statistics for primary and secondary outcomes across different menstrual cycle phases. We will conduct hypothesis tests (e.g., t-tests, ANOVA) to determine if there are statistically significant crude differences in MS symptom severity or relapse rates among different menstrual cycle phases and explore the relationship between the timing of the menstrual cycle and MS symptom severity using correlation coefficients (e.g., Pearson's correlation). We will perform regression analysis to identify any potential predictors of MS symptom severity, including menstrual cycle phase, age, duration of MS, and other relevant covariates and stratify the analysis by age groups to explore for effect modification by reproductive stage of youth, early adulthood (reproductive years) and later adulthood (peri-menopause), respectively defined as participants < 20 years old, 20 to 40 years old, > 40 years old. We will control for potential confounding variables, such as medication use, comorbidities, and lifestyle factors, in these adjusted models. Finally, we will perform sensitivity analysis to assess the robustness of the results by varying assumptions or analytical methods. Finally, we will provide descriptive measures of baseline characteristics/demographics.

Feasibility:

This study will be carried out through the reciprocal ethics process at the Universities of Alberta and Calgary. Each MS Clinic at each clinic follows about 5000 PwMS in Alberta. MS affects 3 women to every man, with average onset between ages 20 to 40. Therefore, both clinics see many women with MS who are at ages who experience menarche.

Timelines:

2 years, each site to recruit 150 participants maximum

What this study adds:

Despite the longstanding knowledge of MS risk, onset, and inflammatory activity being related to different hormonal periods throughout women’s lives, there is still much that is unknown about the interactions and relationship of female hormones and different

female hormonal states upon MS. In addition, women with MS often report MS symptoms as fluctuating in severity at different points throughout their menstrual cycles. However, despite reporting, literature has not shown definitive correlations between MS symptom severity in relation to different points in the menstrual cycle. If we are able to establish correlations between common MS symptoms at particular points in the menstrual cycle, this will aid researchers, clinicians, and women living with MS around examining different strategies to try to treat MS symptom severity at different points throughout the menstrual cycle. This could include strategies such as that seen with perimenstrual migraine, where women enact prophylactic strategies around the time of menstruation to minimize their migraine headaches during that time of the cycle. [48]

Methodologic Issues:

Patients will self-enroll in the study, through accessing and downloading the app as per instruction. Participants download the My Normative App and become a registered user. Once registered, they will read the consent and then sign consent if they wish to participate in the study. Participants will have the option of withdrawing from the study at any time by simply not responding to cues from the app to fill out their questionnaires. Participants are provided with contact information for the study team, and can withdraw from the study by contacting the study team.

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