Title

Comparison of MS inflammatory activity in women using continuous versus cyclic combined oral contraceptives

Authors

Chen, Chelsea S
Krishnakumar, Tanya
Rowles, William
et al.

Publication Date

2020-06-01

DOI

10.1016/j.msard.2020.101970

Peer reviewed

Multiple Sclerosis and Related Disorders 41 (2020) 101970

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Comparison of MS inflammatory activity in women using continuous versus cyclic combined oral contraceptives

Chelsea S. Chen, Tanya Krishnakumar, William Rowles, Annika Anderson, Chao Zhao, Lynn Do, Riley Bove*

Weill Institute for the Neurosciences, Department of Neurology, University of California, San Francisco, CA, United States

ARTICLE INFO

Keywords:
Multiple sclerosis
Oral contraceptive
Hormone
Estrogen
Progestin

ABSTRACT

Background: Many women with multiple sclerosis (MS) report fluctuating symptoms across their menstrual cycle. Oral contraceptives (OCs) alter hormonal levels across the menstrual cycle. While cyclic OCs administer hormones for 21 days, followed by a week of placebo, continuous OCs can administer continuous doses of hormones for up to 3 months. Previous studies have suggested that OC use is associated with lower MS-related inflammation. We hypothesized that due to reduced hormonal fluctuations, women with MS might experience less inflammatory activity (clinical relapses + MRI) on continuous OCs than on cyclic OCs.

Methods: We performed a retrospective analysis of prospectively collected data. For women with MS aged 18–50 seen at the UCSF Center for MS and Neuroinflammation, we extracted data on OC use from the Electronic Medical Records (EMR). All variables were confirmed using manual clinical chart review. We identified 19 women with relapsing forms of MS on continuous OCs and matched them (2:1 when possible) to women on cyclic OCs for OC formulation, age, MS duration and DMT type. Inflammatory activity in the two groups was then compared using log-rank tests (time to new relapse, new T2-weighted lesion formation, and gadolinium-enhancing lesion formation) and t-tests (annualized relapse rate). We also performed subgroup analyses in women with at least 1 year ($N = 28$) and 2 years ($N = 21$) of clinical observation. A power calculation was performed.

Results: There was no difference in time to relapse ($p = 0.50$) between continuous and cycling OC users. However, continuous OC users showed a statistical trend to longer time to T2 lesion formation ($p = 0.09$) and longer time to contrast-enhancing lesion formation ($p = 0.05$). In patients with at least 1 year of observation, there was a significant difference in time to T2 lesion formation ($p = 0.03$) and time to contrast-enhancing lesion formation ($p = 0.02$).

Conclusion: In this exploratory study, women on continuous OCs showed a trend towards less inflammatory activity on MRI relative to women on cyclic OCs. This difference was not reflected in relapse rates. We estimate that 342 patients would be required for an adequately powered cohort study to evaluate such an effect. Our findings provide reassurance that for women using continuous OCs to alleviate menstrual fluctuations in symptoms, there is not an increase in MS-related inflammatory activity.

1. Introduction

Many women with multiple sclerosis (MS) report fluctuating symptoms across their menstrual cycle (Zorgdrager and De Keyser, 1997). It is unclear whether these fluctuations correlate with MS inflammatory activity (Bansil et al., 1999; Holmqvist et al., 2009; Pozzilli et al., 1999), or with other physiological mechanisms, such as fluid shifts, pain sensitivity, or other neural mechanisms (De Bondt et al., 2015a; De Bondt et al., 2015b). There do appear to be differences in immune cell relative distribution and response throughout the menstrual cycle. For example, during the follicular phase there is a decrease in neutrophilic phagocytic activity and in the number of monocyte extracellular traps in peripheral blood compared to the luteal phase (Smirnova et al., 2018). There also appears to be differential Th1 cytokine production and Th2 response suppression across the menstrual cycle (Oertelt-Prigione, 2012). These differences could partially explain the reported increase in MS exacerbations during the premenstrual period (Zorgdrager and De Keyser, 2002). Hormones may also have an

* Corresponding author at: Weill Institute for the Neurosciences, UCSF Department of Neurology, 675 Nelson Rising Lane, San Francisco, CA, United States.
E-mail addresses: chelsea.chen@ucsf.edu (C.S. Chen), tanya.krishnakumar@ucsf.edu (T. Krishnakumar), william.rowles@ucsf.edu (W. Rowles), annika.anderson@ucsf.edu (A. Anderson), chao.zhao@ucsf.edu (C. Zhao), lvtieu@gmail.com (L. Do), riley.bove@ucsf.edu (R. Bove).

https://doi.org/10.1016/j.msard.2020.101970
Received 4 August 2019; Received in revised form 28 December 2019; Accepted 26 January 2020

impact on radiographic MS activity, as higher estradiol serum concentrations have been associated with a greater number of gadolinium-enhancing lesions (Bansil et al., 1999).

Previous studies have suggested that oral contraceptive (OC) use is associated with lower MS-related inflammatory activity (Pozzilli et al., 2015). OCs are one of the most widely-used methods of contraception in the United States (Daniels and Abma, 2018) and rely on scheduled doses of hormones. OCs can be categorized into two major dose types: cyclic and continuous. Cyclic OCs provide 21 days of synthetic estrogen and/or progesterone (Edelman et al., 2014). On the other hand, continuous OCs provide up to 3 months of synthetic estrogen, progesterone, or both (Daniels and Abma, 2018), and limit fluctuations in hormonal levels. Continuous OCs may reduce fluctuations in symptoms such as headaches and pain.

In this single-center retrospective analysis of prospectively collected data, we aimed to assess if differences in OC type (continuous combined vs. cyclic combined) are associated with differences in MS inflammatory activity. We hypothesized that due to reduced hormonal fluctuations, women with MS might experience less marked fluctuations in immunological activity, and hence less MS inflammatory activity on continuous OCs than on cyclic OCs. Therefore, we assessed whether women on continuous combined OCs differed in MS inflammatory activity (relapses and lesions on MRI) from women on cyclic combined OCs.

2. Materials and methods

2.1. Subject selection

From the University of California, San Francisco (UCSF's) Electronic Medical Record (EMR) database, we searched for all women aged 18–50 with a diagnosis of relapsing MS or clinically-isolated syndrome (CIS) seen in our UCSF Center for Multiple Sclerosis and Neuroinflammation between 2009 and 2019, and whose medication list included oral contraceptives (Supplementary Figure 1). We then focused our search on all women with a history of use of continuous combination levonorgestrel + ethinyl estradiol OC. We identified 19 women. For our comparison group, we then identified women aged 18–50 with relapsing MS/CIS and a history of cyclic combination OC (levonorgestrel + ethinyl estradiol, norgestimate + ethinyl estradiol, or norgestrel + ethinyl estradiol) use (see Supplementary Table 1). We included norgestrel and norgestimate in the comparison group due to their similarities to levonorgestrel in their progestogenic, estrogenic, and androgenic properties (Edelman et al., 2014). We matched the women on cyclic OCs to the women on continuous OCs 1:1, and when possible 2:1, by age at the start of observation (± 5 years), disease duration at the start of observation (began at ± 3 years but liberalized to 8 years to allow $N > 15$ in each group), disease-modifying therapy (DMT) at the start of observation, and estrogen and progestin dose (see Supplementary Table 1). DMT groups were defined by efficacy (see Table 1). The start of observation was defined as the first documented date in which the women were taking an eligible OC, had clinically-definite MS or CIS, and were on a disease-modifying therapy (if applicable). The end of observation was defined as the last date in which the given OC was documented as being taken. Match criteria and OC use were verified using clinical chart review. All patients were taking an eligible combination OC during the entire period of observation (Supplementary Table 2).

2.2. MS inflammatory activity outcomes

Patients seen at the UCSF Center for MS and Neuroinflammation are seen by their MS physician twice yearly and undergo an MRI annually. We collected clinical relapses prospectively documented in the clinical notes, as well as radiology reports of the presence of new T2-weighted lesions on serial brain MRIs (available for 27/46), as well as gadolinium-enhancing lesions.

Table 1
Baseline demographic and clinical characteristics for women with MS on continuous as well as cyclic oral contraceptives (OCs). There were no significant differences in any baseline characteristics between the two groups ($p > 0.10$).

	Continuous OCs	Cyclic OCs	All Patients
N	19	27	46
Baseline characteristics			
Age, years (mean, SD)	36.5 (7.1)	35.0 (7.4)	35.6 (7.2)
MS type at observation start			
CIS	1	1	2
RRMS	18	26	44
Disease duration, years (mean, SD)	5.7 (5.4)	6.4 (5.6)	6.2 (5.5)
EDSS (median, IQR)	1.5 (1.0-2.0)	1.5 (1.0-2.0)	1.5 (1.0-2.0)
DMT			
Total lower-efficacy DMT	6	4	10
Interferons	4	1	5
Glatiramer acetate	1	3	4
Teriflunomide	1	1	2
Total medium-efficacy DMT	7	13	20
Dimethyl fumarate	4	8	12
Fingolimod	3	5	8
Total high-efficacy DMT	3	6	9
Rituximab	0	1	1
Natalizumab	2	5	7
Alemtuzumab	1	0	1
No DMT	3	3	6
Observation period, years (mean, SD)	2.9 (2.6)	2.0 (1.6)	2.4 (2.1)
Reason for observation discontinuation			
Switched DMT	1	8	10
Last clinical visit on record	10	11	21
No longer taking OC	4	6	10
Switch to different OC	2	2	4
Pregnancy planning	1	0	1
Age no longer meets study criteria	1	0	1
Total number of MRIs available during observation window	43	32	75
Average time interval between MRIs (years)	1.45	1.96	1.75
Number of patients with MRIs available during observation window	12	15	27

2.3. Analyses

To compare baseline demographic and clinical data between women using continuous vs. cyclic OCs, we used *t*-tests, ANOVA and chi-squared analyses. To compare MS inflammatory activity between the continuous and cyclic OC groups over the observation period, we used log-rank tests (time to new relapse, time to new T2-weighted lesion formation, time to gadolinium-enhancing lesion) and t-tests (annualized relapse rate (ARR) defined as the average number of relapses within one year). We performed sub-analyses with only women with at least 1 year ($N = 13$ continuous and 17 cyclic) and at least 2 years ($N = 11$ and 12) of clinical follow-up. All analyses were performed using the R statistical software's *survival, survminer*, and *pwr* packages.

3. Results

Overall, mean (SD) age of the 46 participants was 35.6 (7.2) years, mean (SD) MS duration was 6.2 (5.5) years, and median (SD, IQR) EDSS (Expanded Disability Status Scale) was 1.5 (1.2, 1.0–2.0) at start of the observation period (Table 1). There was no significant difference between the continuous and cyclic OC groups in any of the baseline characteristics ($p > 0.10$ for each); this was true also for the smaller

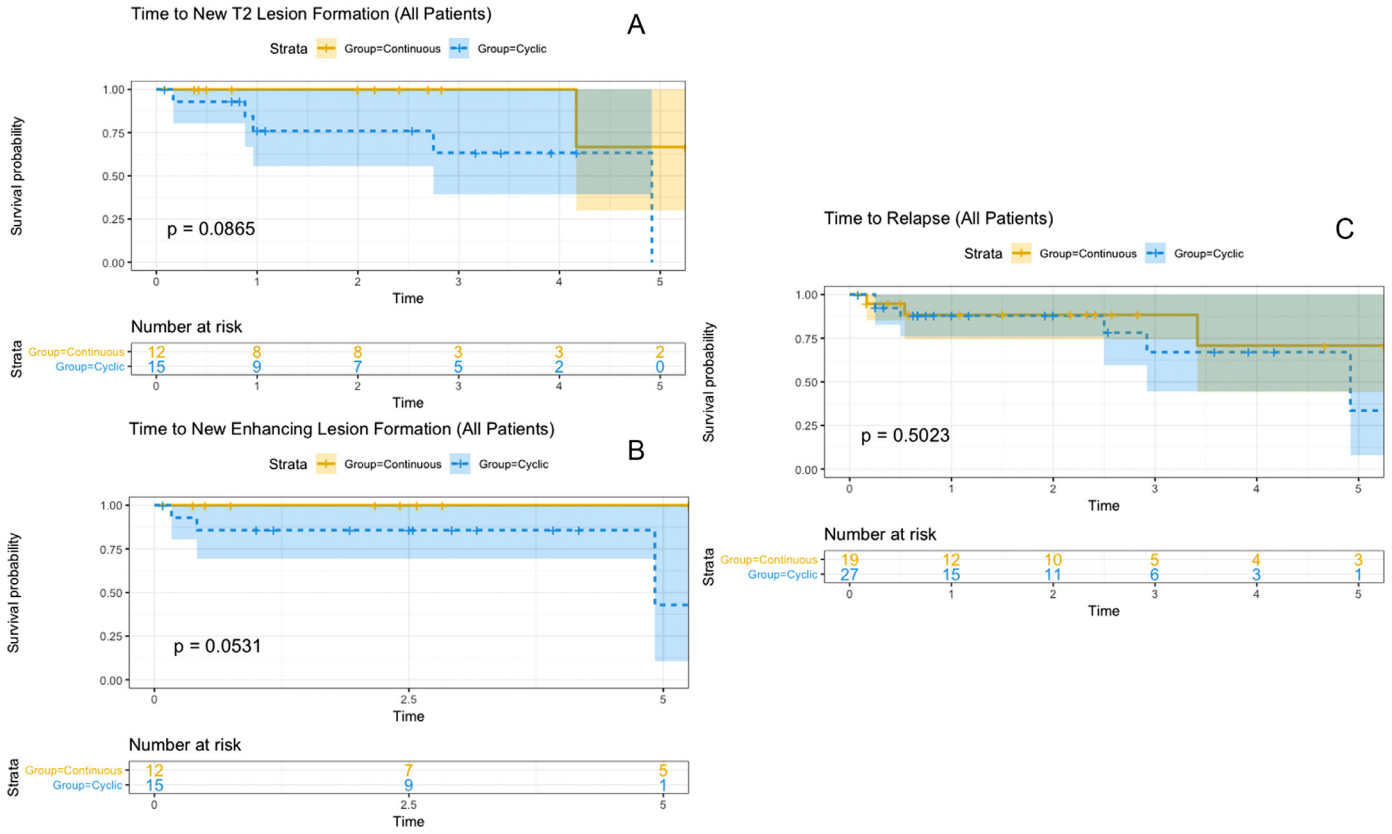

Fig. 1. Survival analysis comparing time to (A) new T2-weighted lesion formation (p = 0.09), (B) contrast-enhancing lesion formation (p = 0.05), and (C) new clinical relapse (p = 0.50) between women with MS/CIS on continuous vs. cyclic oral contraceptives. Analysis truncated at 5 years of observation due to data missingness thereafter.

groups of women with 1 and 2 years of clinical follow up (Supplementary Tables 2 and 3). However, it is noted that the percentage of patients taking low-efficacy DMTs is much lower in the cyclic OC group than the continuous OC group. In patients with 1+ years of observation, this was 23.5% for the cyclic group versus 30.8% for the continuous group (Supplementary Table 2). In patients with 2+ years of observation, this was 25% for the cyclic group versus 18.2% for the continuous group. During the observation period, ARR was 0.10 and relapse count ranged from 0 to 1 per individual. Overall, 22.2% (6/27) of women with MRIs available developed a new T2-weighted lesion, and 11.1% (3/27) developed a new contrast enhancing lesion.

With respect to clinical inflammatory activity, there was no difference in time to new relapse (p = 0.50) or annualized relapse rate (p = 0.66) over the observation period in either the entire group, or in the smaller cohorts with at least one year (N = 28, p = 0.37 and 0.27, respectively) or two years (N = 21, p = 0.50 and 0.54, respectively) of clinical follow up.

However, women on continuous OCs showed a longer time to next contrast-enhancing lesion, both in the entire group (p = 0.05, Fig. 1) and in the smaller cohorts with at least 1 year (p = 0.03, Supplementary Fig. 2) and 2 years (p = 0.02, Supplementary Figure 3) of follow up. Continuous OC users also showed a statistical trend towards a longer time to new T2-weighted lesion formation (p = 0.09, Fig. 1); notable in the groups with 1 year (p = 0.03, Supplementary Fig. 2) but not two years (p = 0.12, Supplementary Fig. 3) of follow up.

When analyzed as univariate Cox proportional regressions, relative to women in cyclic OCs, women on continuous OC had lower hazard ratio for time to relapse (hazard ratio 1.35 (0.3-6.2, p = 0.70), T2-weighted lesion formation (hazard ratio 5.28 (0.6–46.5, p = 0.13) and time to contrast-enhancing lesion formation (2.38 (0–∞, p = 1.00).

4. Discussion

In the current observational study, there was a statistical trend towards lower MRI inflammatory activity in women taking continuous OCs relative to women on cyclic OCs, although there were no differences in clinical relapse rate.

There were important limitations to the current exploratory study, the most obvious of which is the small sample size due to low overall prescription rates of continuous OCs, made even smaller by the lower proportion of patients with MRIs available during this time period. Second, relapses could have been under-ascertained as they were retrospectively collected by clinicians every 6 months. Third, there may be discrepancies between reported OC use in the EMR and actual OC use, including adherence. OC usage in the UCSF EMR database was lower than typically reported in the general American population, (11.7% vs. 17.4% on OCs, (Jones et al., 2012)), perhaps reflecting either under-ascertainment by clinicians in specialized (vs. general medicine) clinics, or trends in OC use among women with MS. Additionally, at least 304 OC brands were recorded, many for the same hormone doses. While we stringently matched and compared OCs based on hormone doses and similarities in endocrine effects, there may be other differences between various brands of similar formulation. We only examined patients using combined OCs in our study, so it is unclear whether the observed results are related to estrogen, progestin, or their combination. Previous studies have suggested that progestins may play a role in reducing inflammation (Benlloch-Navarro et al, 2019), and therefore even small variations in progestin content of COC formulations could play a role. Additionally, we did not evaluate possibly modulatory effects of genetics or adipokines and other endocrine factors, on the relationship between COCs and inflammatory activity. Finally, as this was an observational study, we did not regulate the frequency of clinical visits or

MRIs. Therefore, the dates for the observation periods used were dependent on patients' motivation and ability to visit their providers. We did note an overall shorter period of observation for the cyclic OC users, which was mostly truncated due to the end date being the date of the last UCSF Center for MS and Neuroinflammation visit on record.

While these exploratory findings are far from conclusive, they do provide reassurance that for women with MS on OCs who opt for continuous over cyclic formulations (for e.g., to stabilize symptoms such as pain or headaches (Edelman et al., 2014)), these likely do not pose an increased risk of inflammation relative to more commonly used cyclic OCs. Based on the statistical trends in the current exploratory study, a 1:1 matched prospective cohort study, in which formulations and frequency of evaluations would be harmonized, and adherence monitored, is warranted. While we found small effects of OC type on T2-weighted lesion formation and gadolinium-enhancing lesion formation, we estimate that 342 patients would be required for an adequately powered observational study to evaluate whether women with MS who use continuous OCs do indeed experience lower inflammatory activity.

CRediT authorship contribution statement

Chelsea S. Chen: Conceptualization, Data curation, Formal analysis, Writing - original draft. **Tanya Krishnakumar:** Data curation, Formal analysis, Writing - review & editing. **William Rowles:** Writing - review & editing. **Annika Anderson:** Data curation, Writing - review & editing. **Chao Zhao:** Formal analysis, Writing - review & editing, Methodology, Validation. **Lynn Do:** Writing - review & editing. **Riley Bove:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

Acknowledgements

The authors wish to thank the clinicians and patients of the UCSF Center for MS and Neuroinflammation.

Funding

This study was funded by the National Multiple Sclerosis Society Career Transition Award TA 3062-A-3 (RB).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2020.101970.

References

Bansil, S., Lee, H.J., Jindal, S., Holtz, C.R., Cook, S.D., 1999. Correlation between sex hormones and magnetic resonance imaging lesions in multiple sclerosis. Acta Neurol. Scand 99 (2), 91–94.

Benlloch-Navarro, S., Trachsel-Moncho, L., Fernández-Carbonell, Á., Olivar, T., Soria, J.M., Almansa, I., Miranda, M., 2019. Progesterone anti-inflammatory properties in hereditary retinal degeneration. J. Steroid Biochem. Mol. Biol. 189, 291–301. https://doi.org/10.1016/j.jsbmb.2019.01.007.

Daniels, K., Abma, J.C., 2018. Current Contraceptive Status Among Women Aged 15–49. United States, 2015–2017 8.

De Bondt, T., De Belder, F., Vanhevel, F., Jacquemyn, Y., Parizel, P.M., 2015a. Prefrontal GABA concentration changes in women-Influence of menstrual cycle phase, hormonal contraceptive use, and correlation with premenstrual symptoms. Brain Res. 1597, 129–138.

De Bondt, T., Smeets, D., Pullens, P., Van Hecke, W., Jacquemyn, Y., Parizel, P.M., 2015b. Stability of resting state networks in the female brain during hormonal changes and their relation to premenstrual symptoms. Brain Res. 1624, 275–285.

Edelman, A., Micks, E., Gallo, M.F., Jensen, J.T., Grimes, D.A., 2014. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. Cochrane Database Syst. Rev.(7), Cd004695.

Holmqvist, P., Hammar, M., Landtblom, A.M., Brynhildsen, J., 2009. Symptoms of multiple sclerosis in women in relation to cyclical hormone changes. Eur. J. Contracept. Reprod. Health Care 14 (5), 365–370.

Jones, J., Mosher, W., Daniels, K., 2012. Current contraceptive use in the United States, 2006-2010, and changes in patterns of use since 1995. Nat. Health Stat. Rep. (60), 1–25.

Oertelt-Prigione, S., 2012. Immunology and the menstrual cycle. Autoimmun. Rev. 11 (6-7), A486–A492.

Pozzilli, C., De Giglio, L., Barletta, V.T., Marinelli, F., Angelis, F.D., Gallo, V., Pagano, V.A., Marini, S., Piattella, M.C., Tomassini, V., Pantano, P., 2015. Oral contraceptives combined with interferon beta in multiple sclerosis. Neurol. Neuroimmunol. Neuroinflamm. 2 (4), e120.

Pozzilli, C., Falaschi, P., Mainero, C., Martocchia, A., D'Urso, R., Proietti, A., Frontoni, M., Bastianello, S., Filippi, M., 1999. MRI in multiple sclerosis during the menstrual cycle: relationship with sex hormone patterns. Neurology 53 (3), 622–624.

Smirnova, T.G., Savochkina, A.Y., Dolgushin, I.I., Nikushkina, K.V., Samuseva, I.V., 2018. Changes in functional activity of neutrophils and monocytes isolated from the peripheral blood of women at different phases of the menstrual cycle. Bull. Exp. Biol. Med. 166 (2), 222–224.

Zorgdrager, A., De Keyser, J., 1997. Menstrually related worsening of symptoms in multiple sclerosis. J. Neurol. Sci. 149 (1), 95–97.

Zorgdrager, A., De Keyser, J., 2002. The premenstrual period and exacerbations in multiple sclerosis. Eur. Neurol. 48 (4), 204–206.