

# Linköping University Post Print

## Age at onset of multiple sclerosis is correlated to use of combined oral contraceptives and childbirth before diagnosis

Per Holmqvist, Mats Hammar, Anne-Marie Landtblom and Jan Brynhildsen

N.B.: When citing this work, cite the original article.

Original Publication:

Per Holmqvist, Mats Hammar, Anne-Marie Landtblom and Jan Brynhildsen, Age at onset of multiple sclerosis is correlated to use of combined oral contraceptives and childbirth before diagnosis, 2010, *Fertility and Sterility*, (94), 7, 2835-2837.

<http://dx.doi.org/10.1016/j.fertnstert.2010.06.045>

Copyright: Elsevier Science B.V., Amsterdam.

<http://www.elsevier.com/>

Postprint available at: Linköping University Electronic Press

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-63156>

Running Title:

Combined Oral Contraceptives and MS

# **The age at onset of Multiple Sclerosis is correlated to use of combined oral contraceptives and childbirth before diagnosis**

**\* \*\*Per Holmqvist MD, \*Mats Hammar MD, PhD,**

**\*\*\*A-M Landtblom MD, PhD, \*Jan Brynhildsen MD, PhD**

\* Womens and Childrens Health, \*\*\* Neurology, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, S-581 85 Linköping, Sweden.

\*\* Clinical Department of Obstetrics & Gynaecology, County Hospital Sundsvall, Sweden

Corresponding author:

Per Holmqvist

Clinical Department of Obstetrics & Gynaecology,

County Hospital

SE-85186 Sundsvall, Sweden

Tel: +4660181000

Fax: +4660181557

e-mail: [per.holmqvist@lvn.se](mailto:per.holmqvist@lvn.se)

## **CAPSULE**

The results from a register study showed that the use of oral contraceptives and childbirth was related to the age at onset of Multiple Sclerosis.

## **ABSTRACT**

The aim was to evaluate if the age of onset of Multiple Sclerosis (MS) is related to use of combined oral contraceptives (COC) and/or timing of childbirth. The results showed that use of COC and childbirth before the first MS symptom was correlated to a higher mean age at the onset of the disease.

Multiple sclerosis (MS) is an autoimmune disease of the CNS, characterized by inflammation, myelin damage, gliosis, axonal and oligodendrocyte pathology and progressive neurological symptoms. Experimental Autoimmune Encephalomyelitis (EAE) is the dominant animal model for MS. Studies of EAE and MS have suggested that the balance between pro-inflammatory T helper cells type 1 (Th1) and anti-inflammatory T helper cells type 2 (Th2) is crucial for the immunopathology with a Th1 domination during exacerbations and a Th2 activity during remission(1-2).

Studies indicate that sex hormones may influence the pathogenesis and course of MS. Hence the prevalence in MS is two to three times higher in women than in men(3) and the disease course seems to differ between the sexes.(4-5).

During pregnancy both clinical symptoms and relapse rate of MS seem to decrease while the post-partum period is associated with a risk for exacerbation of the disease (6-11). The amelioration of MS during pregnancy is associated with several changes of the immune system, which are believed to be a result of very high levels of estrogens and progesterone but also of other hormones as 1,25-dihydroxy-vitamin D<sub>3</sub>, norepinephrine and cortisol(12-15).

Magnetic Resonance Imaging (MRI) is the most important imaging method used to diagnose and evaluate the progression of MS. Changes in disease activity on MRI scans have been shown to be related to female steroid sex hormones although the results are partially contradictory (16-17).

Because activity of MS seems to be in some way related to sex steroid levels, treatment with sex steroids has been suggested. Studies of EAE have shown that estrogen treatment before induction of EAE can delay onset of the disease and reduce disease activity. (18-23). Studies of treatment with estrogens after onset of EAE have shown contradictory results. Interestingly

though, orally given  $17\alpha$ -ethinylestradiol, which is the most used estrogen component in combined oral contraceptives, reduced disease severity(24). Sicotte, et al, reported that treatment with the low-potent estrogen estriol, which is produced in high concentrations during pregnancy, decreased the number and volume of MRI-lesions, although this study was not placebo-controlled (25).

Two cohort studies (26-27) failed to show any effect of oral contraceptives (OC) on incidence of MS, however, the type of oral contraceptives was not specified. One case-control study (28), stratified for type of contraceptive used, showed a lower incidence of MS-lesions among users of combined oral contraceptives (COC) compared to non-users. Thus the effect of COCs on MS disease activity has not been thoroughly studied but the results of the latter study(28) indicate a possible positive effect.

The aim of this study was to relate COC use and childbirth to the onset of MS.

The Swedish national MS register (SMS register) is a nationwide quality register that includes a majority of all patients with MS in Sweden, presently about 10 000, with data on age at onset of the first symptoms, characterisation of onset and age at final diagnosis. Moreover, the neurologists prospectively register data about the patients including status, use of medication and EDSS (Expanded Disability Status Scale)(29) scores at each visit. At inclusion in the register all patients are asked for their consent to participate in research including questionnaires and the use of their data in the register.

A questionnaire was sent to all 1009 women in the SMS register with diagnosed MS, living in five counties in Sweden, and being below 46 years of age. The questionnaire comprised questions on

COC-use, pregnancies, childbirth, breast-feeding, medication as well as age at first MS-symptoms and age at MS-diagnosis. When suitable we used categorized answering options.

Data were optically scanned into the computer and optical scanning was checked manually. From the SMS register we collected data regarding age at MS onset according to the woman's neurologist for the women who had returned the questionnaire.

*Statistics:* We used SPSS 16.0 for statistical analyses using Pearson correlation and General Linear Models including ANOVA/ANCOVA.

*Ethics:* This study was approved by the Regional Ethical Committee at the University of Linköping and the Ethical Board of the Swedish MS register.

After one reminder, 837 women (83%) returned the questionnaire. Of these, 770 women had complete data in the SMS register and were included in the statistical analyses. Incongruous data were defined as missing data. In the questionnaire the women defined the age when they had experienced the first symptom of MS, i.e. the probable onset of the disease. This information was also available in the SMS register. The correlation between the different sources of information was high ( $r = 0.879$ ,  $p < .001$ ).

There was a significant difference in mean age at onset for the first MS symptoms between women who had and had not been using COC respectively (26 vs 19 years,  $p < .001$ ). The mean age at onset was higher the longer the women had been using COCs before the onset of MS (Table 1).

The mean age at first MS symptom was 31 years for women who had given birth before the onset of MS and 23 years for women who had not ( $p < .001$ ). For each child born before the onset of MS the age at first MS symptom was higher. In a full factorial General Linear Model analysis, including age at start of COC use, both duration of COC use and number of children

born before the first MS symptom had independent statistically significant effects on age at MS onset.

Table 1. ANOVA table of mean age  $\pm$  SD at onset of Multiple Sclerosis (MS) for groups of the women based on duration of COC use before the first MS symptom.

	<b>Non-user</b>	<b>Less than 1 year</b>	<b>1-3 years</b>	<b>4-5 years</b>	<b>6-10 years</b>	<b>More than 10 years</b>	<b>p</b>
<b>Age at MS onset</b>	19 $\pm$ 5.4	24 $\pm$ 7.3	24 $\pm$ 6.3	25 $\pm$ 5.6	27 $\pm$ 4.4	32 $\pm$ 4.5	< .001

We found that use of COC before the onset of MS was related to a later onset of the disease. This contradicts the results from two previous cohort studies (26-27) but is in accordance with one case-control study (28). In the present study, as well as in the study by Alonso et al (28) COC was clearly defined and a clear relation between COC use and a later onset of MS was revealed. In some of the previous studies (26-28), the wider term “oral contraceptives” has been used and it is unclear whether also users of progestin-only contraceptives have been included in those studies, which in such case may explain the different findings. Our data also show that the longer the women had been using COC the later they experienced their first MS symptom. In agreement with the findings from Alonso et al(28) this suggests a protective effect of COC. We also found a statistically significant positive correlation between number of children born before the first MS symptom and age at MS onset. This is in line with findings from D’hooghe *et al* who recently showed that a slower progression of MS occurred in women who had given birth(30). Previous studies have shown a positive effect of pregnancy on MS disease activity (6-10). This effect has been suggested to be due to high levels of circulating estrogens and their effect on the immune system.(12-15) The more term pregnancies a woman has gone through, the longer the total duration of high estrogen exposure and possibly a longer potential protection from MS pathophysiology.

It could be argued that the later the woman has had her onset of MS, the longer is the possible time been that she could have been exposed to COC and pregnancies. This argument is in the present study contradicted by the difference in the mean age at MS onset between the groups of women. The difference in mean age at MS onset was 5 years between women who had not used COC and women who reported use of COC for less than one year (table 1). Between the “less than one year”-group and the “1-3 years”-group there was no difference in mean age at MS onset. The women who reported 4-5 years of COC use had only one year higher mean age at MS onset than the women who reported less than one year of COC use. If the duration of COC use would be longer the higher the age at MS onset, these differences most probably would have been much larger. We also used a General Linear Model which included analysis of covariances with number of children born before MS onset and age at start of COC use. The study-design with a questionnaire always brings along a risk of recall-bias. Because of this we used categorized answers in questions regarding duration of COC use. The recall-bias problem could also affect the women’s answer on the question about the age at first MS symptom. The answers in the questionnaire, however, correlated well with the information in the SMS register.

We speculate that the women studied, who all have developed MS in the end, have a susceptibility to the disease but that the differences in use of COC and number of term pregnancies before MS onset, at least partially, might have influenced the age at MS onset through the effects of estrogens on the immune system. Our results indicate a protective effect of COC and childbirth on MS. If a protective effect of COC could be found on the progress of the disease, this information should be highly relevant when counselling this group of women both for their disease and for contraception.

## ACKNOWLEDGEMENTS

Gunn Johansson, Department of Neurology, University Hospital of Linköping, Sweden for technical assistance.

Erling Englund, Msc and Mats Fredriksson, PhD for statistical advice

Leszek Stawiarz at the Swedish National MS register (MS regisiter).

## REFERENCES

1. Correale, J, Gilmore, W, McMillan, M, Li, S, McCarthy, K, Le, T, et al. Patterns of cytokine secretion by autoreactive proteolipid protein-specific T cell clones during the course of multiple sclerosis. *J Immunol.* 1995; 154:2959-68.
2. Zamvil, SS, Steinman, L. The T lymphocyte in experimental allergic encephalomyelitis. *Annu Rev Immunol.* 1990; 8:579-621.
3. Orton, SM, Herrera, BM, Yee, IM, Valdar, W, Ramagopalan, SV, Sadovnick, AD, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. *Lancet Neurol.* 2006; 5:932-6.
4. Pozzilli, C, Tomassini, V, Marinelli, F, Paolillo, A, Gasperini, C, Bastianello, S. 'Gender gap' in multiple sclerosis: magnetic resonance imaging evidence. *Eur J Neurol.* 2003; 10:95-7.
5. Duquette, P, Girard, M. Hormonal factors in susceptibility to multiple sclerosis. *Curr Opin Neurol Neurosurg.* 1993; 6:195-201.
6. Bernardi, S, Grasso, MG, Bertollini, R, Orzi, F, Fieschi, C. The influence of pregnancy on relapses in multiple sclerosis: a cohort study. *Acta Neurol Scand.* 1991; 84:403-6.
7. Confavreux, C, Hutchinson, M, Hours, MM, Cortinovis-Tourniaire, P, Moreau, T. Rate of pregnancy-related relapse in multiple sclerosis. *Pregnancy in Multiple Sclerosis Group. N Engl J Med.* 1998; 339:285-91.
8. Damek, DM, Shuster, EA. Pregnancy and multiple sclerosis. *Mayo Clin Proc.* 1997; 72(9):977-89.
9. Houtchens, MK. Pregnancy and multiple sclerosis. *Semin Neurol.* 2007; 27:434-41.
10. Hutchinson, M. Pregnancy in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 1993; 56:1043-5.
11. Vukusic, S, Hutchinson, M, Hours, M, Moreau, T, Cortinovis-Tourniaire, P, Adeleine, P, et al. Pregnancy and multiple sclerosis (the PRIMIS study): clinical predictors of post-partum relapse. *Brain.* 2004; 127:1353-60.
12. Elenkov, IJ, Wilder, RL, Bakalov, VK, Link, AA, Dimitrov, MA, Fisher, S, et al. IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: implications for autoimmune disease activity during these times. *J Clin Endocrinol Metab.* 2001; 86:4933-8.

13. Sanchez-Ramon, S, Navarro, AJ, Aristimuno, C, Rodriguez-Mahou, M, Bellon, JM, Fernandez-Cruz, E, et al. Pregnancy-induced expansion of regulatory T-lymphocytes may mediate protection to multiple sclerosis activity. *Immunol Lett.* 2005; 96:195-201.
14. Saraste, M, Vaisanen, S, Alanen, A, Airas, L. Clinical and immunologic evaluation of women with multiple sclerosis during and after pregnancy. *Gend Med.* 2007; 4:45-55.
15. Formby, B. Immunologic response in pregnancy. Its role in endocrine disorders of pregnancy and influence on the course of maternal autoimmune diseases. *Endocrinol Metab Clin North Am.* 1995; 24:187-205.
16. Pozzilli, C, Falaschi, P, Mainero, C, Martocchia, A, D'Urso, R, Proietti, A, et al. MRI in multiple sclerosis during the menstrual cycle: relationship with sex hormone patterns. *Neurology.* 1999; 53:622-4.
17. Bansil, S, Lee, HJ, Jindal, S, Holtz, CR, Cook, SD. Correlation between sex hormones and magnetic resonance imaging lesions in multiple sclerosis. *Acta Neurol Scand.* 1999; 99:91-4.
18. Ito, A, Buenafe, AC, Matejuk, A, Zamora, A, Silverman, M, Dwyer, J, et al. Estrogen inhibits systemic T cell expression of TNF-alpha and recruitment of TNF-alpha(+) T cells and macrophages into the CNS of mice developing experimental encephalomyelitis. *Clin Immunol.* 2002; 102:275-82.
19. Kim, S, Liva, SM, Dalal, MA, Verity, MA, Voskuhl, RR. Estriol ameliorates autoimmune demyelinating disease: implications for multiple sclerosis. *Neurology.* 1999; 52:1230-8.
20. Morales, LB, Loo, KK, Liu, HB, Peterson, C, Tiwari-Woodruff, S, Voskuhl, RR. Treatment with an estrogen receptor alpha ligand is neuroprotective in experimental autoimmune encephalomyelitis. *J Neurosci.* 2006; 26:6823-33.
21. Offner, H. Neuroimmunoprotective effects of estrogen and derivatives in experimental autoimmune encephalomyelitis: therapeutic implications for multiple sclerosis. *J Neurosci Res.* 2004; 78:603-24.
22. Palaszynski, KM, Liu, H, Loo, KK, Voskuhl, RR. Estriol treatment ameliorates disease in males with experimental autoimmune encephalomyelitis: implications for multiple sclerosis. *J Neuroimmunol.* 2004; 149:84-9.
23. Ito, A, Bebo, BF, Jr., Matejuk, A, Zamora, A, Silverman, M, Fyfe-Johnson, A, et al. Estrogen treatment down-regulates TNF-alpha production and reduces the severity of experimental autoimmune encephalomyelitis in cytokine knockout mice. *J Immunol.* 2001; 167:542-52.
24. Subramanian, S, Matejuk, A, Zamora, A, Vandebark, AA, Offner, H. Oral feeding with ethinyl estradiol suppresses and treats experimental autoimmune encephalomyelitis in SJL mice and inhibits the recruitment of inflammatory cells into the central nervous system. *J Immunol.* 2003; 170:1548-55.
25. Sicotte, NL, Liva, SM, Klutch, R, Pfeiffer, P, Bouvier, S, Odesa, S, et al. Treatment of multiple sclerosis with the pregnancy hormone estriol. *Ann Neurol.* 2002; 52:421-8.
26. Hernan, MA, Hohol, MJ, Olek, MJ, Spiegelman, D, Ascherio, A. Oral contraceptives and the incidence of multiple sclerosis. *Neurology.* 2000; 55:848-54.
27. Thorogood, M, Hannaford, PC. The influence of oral contraceptives on the risk of multiple sclerosis. *Br J Obstet Gynaecol.* 1998; 105:1296-9.
28. Alonso, A, Jick, SS, Olek, MJ, Ascherio, A, Jick, H, Hernan, MA. Recent use of oral contraceptives and the risk of multiple sclerosis. *Arch Neurol.* 2005; 62:1362-5.
29. Kurtzke, JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983; 33:1444-52.
30. D'Hooghe M, B, Nagels, G, Uitdehaag, BM. Long-term effects of childbirth in MS. *J Neurol Neurosurg Psychiatry.* 2010; 81:38-41.