Review Article

Pregnancy History, Oral Contraceptive Pills Consumption (OCPs), and Risk of Multiple Sclerosis: A Systematic Review and Meta-Analysis

Mahsa Ghajarzadeh[1,2], Aida Mohammadi[2], Zahra Shahraki[3], Mohammad Ali Sahraian[1], Mehdi Mohammadifar[4]

[1]Multiple Sclerosis Research Center, Neuroscience institute, Tehran University of Medical Sciences, [2]Universal Council of Epidemiology (UCE), Universal Scientific Education and Research Network (USERN), Tehran University of Medical Sciences, Tehra[n], [3]Zabol university o Medical Sciences, Zabol, [4]Department of Radiology, Zanjan University of Medical Sciences, Zanjan, Iran

Abstract

Background: To estimate the pooled odds of oral contraceptive pills consumption (OCPs) use as well as pregnancy history and multiple sclerosis (MS) risk. **Methods:** We systematically searched PubMed, Embase, Scopus, Web of Science, Google scholar, and gray literature including references of the references as well as conference papers. The search strategy in PubMed was ((Oral contraceptive pills) OR OCP) AND (Multiple Sclerosis OR Sclerosis, Multiple) OR Sclerosis, Disseminated) OR Disseminated Sclerosis) OR MS (Multiple Sclerosis)) OR Multiple Sclerosis, Acute Fulminating) AND (gravidity) OR (pregnancy). **Results:** Four studies were included. The pooled odds of developing MS in women with pregnancy history compared with nulligravid women was 0.64 (95%CI = 0.53 − 0.78) (I^2 = 0, P = 0.5), which means that pregnancy reduces the risk of MS by 36%. The pooled odds of OCP consumption and risk of MS were 1.09 (95% CI = 0.67 − 1.76). By comparing the pooled odds of OCP consumption and risk of MS according to the country of the origin, we found that the pooled odds in Iranian studies was 1.03 (95% CI = 0.31 − 3.45) and the pooled OR in studies that were conducted in the United States was 1.13 (95% CI = 0.65 − 1.98), which showed that the country of the origin was not the cause of heterogeneity. **Conclusions:** The results of this systematic review show that pregnancy history is a protective factor for MS development, whereas OCP use has no significant effect.

Keywords: *Multiple sclerosis, oral contraceptive pills, pregnancy, risk*

Introduction

Multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system, is affecting women more than men, with increasing prevalence and incidence all over the world.[1-3] The exact etiology is unknown while genetics and environmental factors such as vitamin D level, smoking, air pollution, and Epstein–Barr virus infection have been considered as predisposing factors.[2,4,5] Women are more affected and female hormones are suggested to play a role in disease development. Women have stronger immune systems with higher levels of immunoglobulins, more activated T cells, and further antibody production after antigen presentation.[6]

Age at menarche, oral contraceptive pills (OCPs) use, pregnancy history, and number of parities are among the possible effective factors of MS development.[7]

A previous systematic review showed that 1-year increase in the age at menarche will decrease the odds of developing MS by 12%.[8]

History of pregnancy has been shown to be a protective factor for developing MS, whereas the magnitude of the effect varies between studies.[7,9,10]

There are controversies regarding the use of OCPs and increasing the risk of MS. A recent case-control study showed that OCP administration for more than 1 year increased the risk of MS by 40%,[7] while Alonso *et al*. reported no association between OCPs use and MS risk (OR = 0.8, 95%CI = 0.55 − 1.25).[9] On the other hand, D'hooghe *et al*.[11] found that women who had used OCPs had more aggressive courses of MS than others without history of OCPs use.

As there are controversies regarding the use of OCPs and the risk of MS as well as the magnitude of pregnancy history on MS development, we aimed to do this systematic review and meta-analysis to estimate the pooled odds of OCPs use as well as pregnancy history and MS risk.

How to cite this article: Ghajarzadeh M, Mohammadi A, Shahraki Z, Ali Sahraian M, Mohammadifar M. Pregnancy history, oral contraceptive pills consumption (OCPs), and risk of multiple sclerosis: A systematic review and meta-analysis. Int J Prev Med 2022;13:89.

Address for correspondence:
Dr. Mahsa Ghajarzadeh, Department of Neurology, Imam Hospital, Tehran, Iran.
E-mail: m.ghajarzadeh@gmail.com

Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.IJPVM_299_20

Quick Response Code:

Methods

We systematically searched PubMed, Embase, Scopus, Web of Science, Google scholar, and gray literature including references of the references as well as conference papers.

Inclusion criteria

Case-control studies, articles providing crude odds ratio of nulli-gravidity and OCP use, and MS or the number of cases and controls who had history of OCP administration and gravidity history.

Exclusion criteria

Cohort, cross-sectional, and review articles.

Search strategy

The search strategy in PubMed was ((Oral contraceptive pills) OR OCP) AND (Multiple Sclerosis OR Sclerosis, Multiple) OR Sclerosis, Disseminated) OR Disseminated Sclerosis) OR MS (Multiple Sclerosis)) OR Multiple Sclerosis, Acute Fulminating) AND (gravidity) OR (pregnancy).

Selecting the studies

The titles of retrieved articles were screened by the second author (A.M.), who excluded those that clearly did not relate to the aim of the study. Then abstracts were assessed by two independent researchers (A.M. and A.A.) and eligible articles were selected.

Data regarding the name of the first authors, publication year, country, number of OCPs users in each group of the study, crude Odds ratio (OR), and 95% CI for pregnancies/parity and OCP consumption were extracted.

Assessment of study quality

We assessed the risk of bias (quality assessment of each article) using the modified NEWCAS-TLE-OTTAWA QUALITY ASSESSMENT SCALE for (case-control studies) Table 1.[12]

Meta-analysis

In this meta-analysis, we estimated pooled OR for the dichotomous variable: using OCP in women and pregnancy history before developing MS. The number of OCP users in both case and control groups was recorded and pooled estimates were calculated. In a study by Rejali *et al*.,[13] they estimated adjusted OR for the number of pregnancies, so we did not include their results for the first analysis [Table 2].

Statistical analysis

We used STATA version 13.0 (Stata Corp LP, College Station, TX, USA) for data analysis. Random effects models were used and heterogeneity was determined by the inconsistency (I^2) calculation.

Results

The first literature search revealed 1,760 articles. After the deletion of duplicate articles, finally, 243 articles were remained. Excluding nonrelevant articles, resulted in including four articles [Figure 1].

We considered the odds of OCP consumption and also the odds of one or more pregnancies. Two studies were from Iran and two from the United States.

In two studies (Salehi and Hellwig), number of parities and in the other study the number of pregnancies were mentioned as we considered both of them as the number of pregnancies. As in Rejali *et al*.[13] study, the adjusted OR for number of pregnancies were mentioned, their result was not included in the first analysis [Table 1].

The pooled odds of developing MS in women with pregnancy history compared with nulli-gravid women was 64% (95% CI = 53%–78%) (I^2 = 0, P = 0.5), which means that gravidity reduces the risk of MS by 36% Figure 2.

The pooled odds of OCP consumption and risk of MS was 1.09 (95% CI = 0.67 − 1.76) (I^2 = 90%, P < 0.001) [Figure 3].

By comparing the pooled odds of OCP consumption and risk of MS according to the country of the origin, we found that the pooled odds in Iranian studies was 1.03 (95% CI = 0.31–3.45) (I^2 = 96%, P < 0.001) and the pooled OR studies which were conducted in the United States was 1.13 (95% CI = 0.65–1.98) (I^2 = 91%, P < 0.001), which showed that the country of origin was not the cause of heterogeneity [Figure 4].

Discussion

To our knowledge, this is the first systematic review and meta-analysis evaluating the role of gravidity and OCP

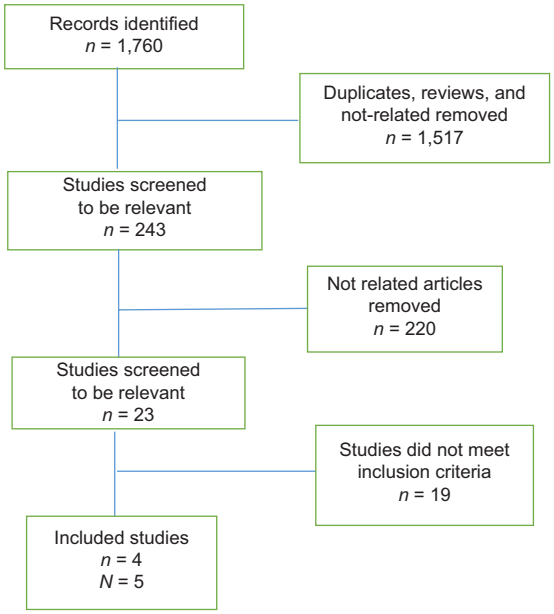

Figure 1: Flow diagram of included studies

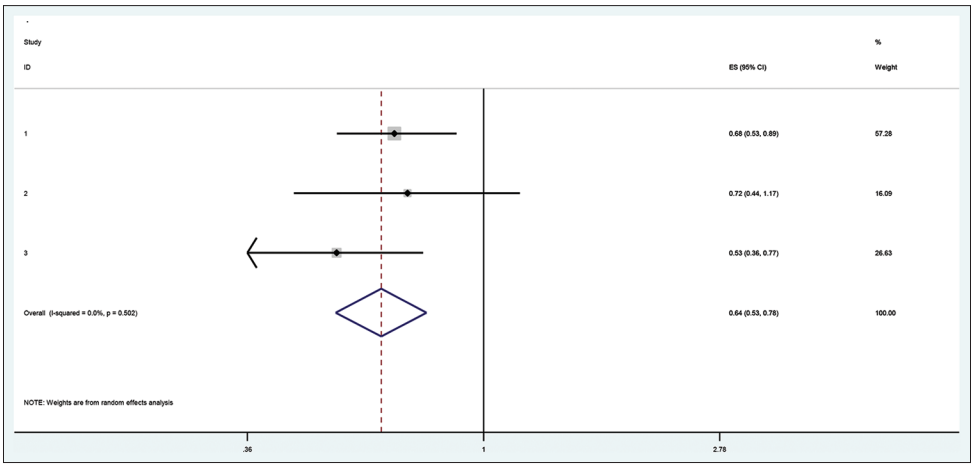

Figure 2: The pooled OR of pregnancy history and risk of MS

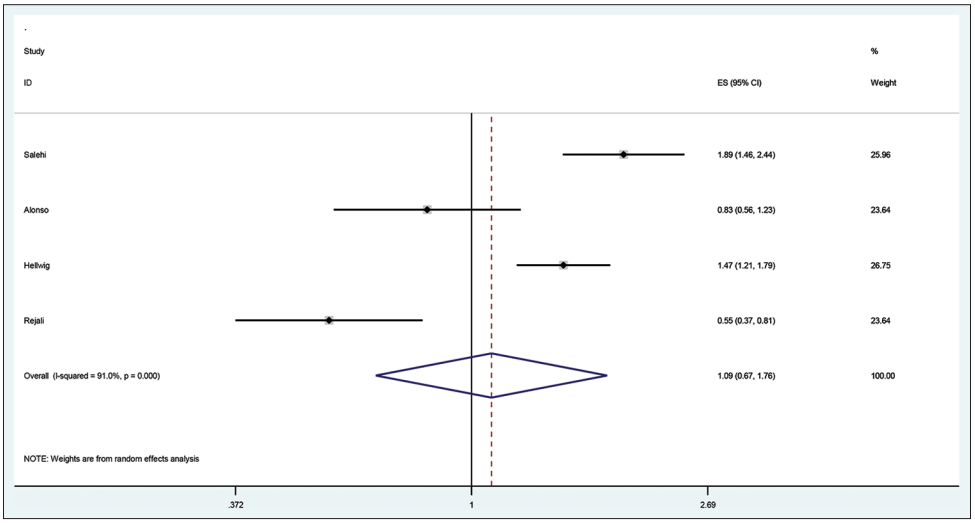

Figure 3: The pooled OR of OCP consumption and risk of MS

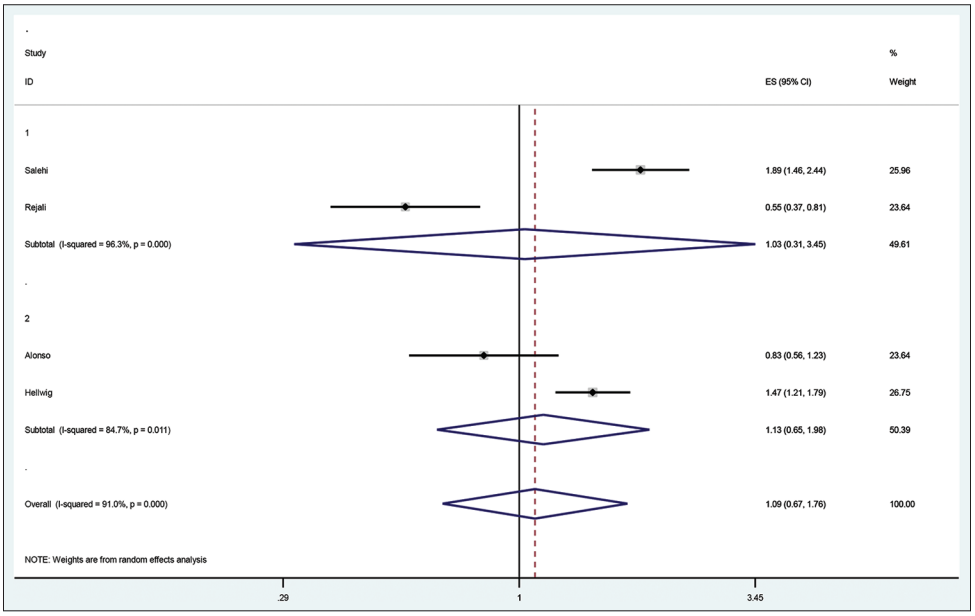

Figure 4: The pooled OR of OCP consumption and risk of MS based on the country of origin

Table 1: Characteristics of included studies

First author	Published year	Country	Type of study	No of OCP consumers in cases	No of OCP consumers in controls	OR (95%CI) for OCP	OR (95%CI) for no of pregnancies
Salehi[7]	2018	Iran	Case-control	226/399	221/541	1.89 (1.45-2.45)	0.61 (0.49-0.75)
Alonso[9]	2005	USA	Case-control	56/106	605/1001	0.83 (0.55-1.25)[9]	0.72 (0.44-1.17)
Hellwig[10]	2016	USA	Case-control	160/400	1260/3940	1.39 (1.13-1.72)	0.53 (0.36-0.77)
Rejali[13]		Iran	Case-control	69/200	97/200	0.55 (0.37-0.83)	-

Table 2: Quality assessment of case-control studies

First author	Case definition	Representativeness	Selection of controls	Definition of controls	Comparability	Ascertainment of exposure	Same method of ascertainment	Nonresponse rate	Score
Salehi	a	a	a	a	a	c	a	A	7
Alonso	a	a	a	a	a	c	a	-	6
Hellwig	a	a	a	a	a	c	a	-	6
Rejali	a	a	a	a	a	c	a	-	6

consumption in MS development. The pooled OR for developing MS in women with pregnancy history compared with nulligravid women was 0.64, which means that gravidity reduces the risk of MS by 36%. The Odds of having pregnancy and MS development ranged from 0.53 to 0.72 in three included studies that could be based on sample size variation and different characteristics of included patients.

Salehi *et al*.[7] enrolled 399 women with MS and 541 healthy women and reported the crude Odds ratio of parity history as 0.68 and the crude odds of number of parities as 0.77.

Alonso *et al*.[9] reported the Odds of 0.8 for women with history of one pregnancy and 1.3 for two or more pregnancies in comparison with women with no history of pregnancy.

Hellwig *et al*.[10] investigated the Odds of 0.53 in women with at least one parity by assessing 239 MS patients and 2,322 healthy women.

Literature shows a protective effect of pregnancy against MS development. A previous study conducted by Holmqvist *et al*.[14] demonstrated that parity could be effective in delaying manifestation of MS symptoms when they compared women with parity history and women with no history of parity. In a cohort study, Nielsen *et al*.[15] found that women with one parity had a 24% reduced risk of MS than women with no parity history. It has been shown that childbearing will reduce the risk of developing MS.[16] On the other hand, Nielsen *et al*.[15] and Magyari *et al*.[17] reported the beneficial effects of the number of parities on the reduction of MS risk.

The role of pregnancy in reducing the risk of MS may be due to modulation of immune system by sex hormones. The literature shows the remission of the disease during pregnancy.[18-20]

Our results also showed that OCP consumption is not related with increased risk of developing MS 1.09 (95% CI = 0.67–1.76).

There are controversies regarding the role of OCPs in developing MS.

In a previous cohort study, Villard-Mackintosh *et al*.[20] found that OCPs use does not decrease the risk of MS development (OR = 0.7, 95% CI = 0.4–1.1), which was in agreement with the results of the Royal College of General Practitioners Oral Contraception Study.[20,21]

Salehi *et al*.[7] reported an increased risk of MS in OCPs users than nonusers (OR = 1.89, 95% CI = 1.45–2.45), which is in line with Hellwig *et al*.[10] results who found an increased risk (OR = 1.39, 95% CI = 1.09–1.96).

D'hooghe *et al*.[11] and Poser *et al*.[22] demonstrated that OCPs administration would increase MS-related disability progression. On the other hand, Alonso and Rejali reported no effect of OCP use on developing MS (OR = 0.83, and OR = 0.55) (the CI of both Odds includes 1).[9,13] Salehi *et al*.[7] also found that by 1-year increase in the age of OCP use the risk of developing MS will decrease by 5% (OR = 0.95, $P = 0.004$).

OCPs contain synthetic estrogen and progesterone and they inhibit the pulsatile release of gonadotropin-releasing hormone and hamper follicular development, which results in un ovulation. There is also evidence that OCPs suppress activating production during the cycle, which has neuroprotective effects and inhibits neural degeneration.[23]

To our knowledge, this study is the first systematic review evaluating the role of pregnancy and OCPs use in MS development.

It has some limitations. First, the number of included studies is limited. Second, the number of cases and controls were not similar in all studies. Third, the I^2 was 91% for pooled OR of OCP use that shows heterogeneity between study results. After subgroup analysis by the country of origin, the heterogeneity still exists.

Conclusions

The results of this systematic review show that pregnancy history is a protective factor for MS development, whereas OCP use has no significant effect.

Declaration

- Ethics approval and consent to participate: N/A
- Consent for publication: Yes
- Authors contributions: All authors read and approved the manuscript
- Availability of data and materials: Not applicable.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 26 May 20 **Accepted:** 01 Dec 20
Published: 24 Jun 22

References

1. Ghajarzadeh M, Jalilian R, Sahraian MA, Moghadasi AN, Azimi A, Mohammadifar M, *et al*. Pain in patients with multiple sclerosis. Maedica 2018;13:125.
2. Ghajarzadeh M, Keshtkar AA, Azimi A, Sahraian MA, Mohammadifar M, Ramagopalan SV. The effect of vitamin D supplements on clinical and para-clinical outcomes in patients with multiple sclerosis: Protocol for a systematic review. JMIR Res Protoc 2019;8:e12045. doi: 10.2196/12045.
3. Sahraian MA, Khorramnia S, Ebrahim MM, Moinfar Z, Lotfi J, Pakdaman H. Multiple sclerosis in Iran: A demographic study of 8,000 patients and changes over time. Eur Neurol 2010;64:331-6.
4. Turk Boru U, Boluk C, Tasdemir M, Gezer T, Serim VA. Air pollution, a possible risk factor for multiple sclerosis. Acta Neurol Scand 2020;141:431-7.
5. Eskandari G, Ghajarzadeh M, Yekaninejad MS, Sahraian MA, Gorji R, Rajaei F, *et al*. Comparison of serum vitamin D level in multiple sclerosis patients, their siblings, and healthy controls. Iran J Neurol 2015;14:81-5.
6. Whitacre CC. Sex differences in autoimmune disease. Nat Immunol 2001;2:777-80.
7. Salehi F, Abdollahpour I, Nedjat S, Sahraian MA, Memari A-H, Rahnama M, *et al*. Uncovering the link between reproductive factors and multiple sclerosis: A case-control study on Iranian females. Mult Scler Relat Disord 2018;20:164-8.
8. Azimi A, Hanaei S, Sahraian MA, Mohammadifar M, Ramagopalan SV, Ghajarzadeh M. Age at menarche and risk of multiple sclerosis (MS): A systematic review and meta-analysis. BMC Neurol 2019;19:1-5.
9. Alonso Á, Jick SS, Olek MJ, Ascherio A, Jick H, Hernán MA. Recent use of oral contraceptives and the risk of multiple sclerosis. Arch Neurol 2005;62:1362-5.
10. Hellwig K, Chen LH, Stancyzk FZ, Langer-Gould AM. Oral contraceptives and multiple sclerosis/clinically isolated syndrome susceptibility. PloS One 2016;11:e0149094. doi: 10.1371/journal.pone. 0149094.
11. D'hooghe M, Haentjens P, Nagels G, D'Hooghe T, De Keyser J. Menarche, oral contraceptives, pregnancy and progression of disability in relapsing onset and progressive onset multiple sclerosis. J Neurol 2012;259:855-61.
12. Lv Y-B, Wang Y, Ma W-G, Yan D-Y, Zheng W-L, Chu C, *et al*. Association of renalase SNPs rs2296545 and rs2576178 with the risk of hypertension: A meta-analysis. PLoS One 2016;11:e0158880. doi: 10.1371/journal.pone. 0158880.
13. Rejali M, Hosseini SM, Tabaee MSK, Etemadifar M. Assessing the risk factors for multiple sclerosis in women of reproductive age suffering the disease in Isfahan Province. Int J Prev Med 2016;7:58.
14. Holmqvist P, Hammar M, Landtblom A-M, Brynhildsen J. Age at onset of multiple sclerosis is correlated to use of combined oral contraceptives and childbirth before diagnosis. Fertil Steril 2010;94:2835-7.
15. Nielsen NM, Jørgensen KT, Stenager E, Jensen A, Pedersen BV, Hjalgrim H, *et al*. Reproductive history and risk of multiple sclerosis. Epidemiology 2011:546-52.
16. Hedström A, Hillert J, Olsson T, Alfredsson L. Reverse causality behind the association between reproductive history and MS. Mult Scler 2014;20:406-11.
17. Magyari M, Koch-Henriksen N, Pfleger CC, Sørensen PS. Reproduction and the risk of multiple sclerosis. Mult Scler 2013;19:1604-9.
18. Whitacre CC, Reingold SC, O'Looney PA, Blankenhorn E, Brinley F, Collier E, *et al*. A gender gap in autoimmunity: Task force on gender, multiple sclerosis and autoimmunity. Science 1999;283:1277-8.
19. American Association for the Advancement of Science. Sex differences in autoimmune disease: Focus on multiple sclerosis. Science 1999;283:1278.
20. Villard-Mackintosh L, Vessey MP. Oral contraceptives and reproductive factors in multiple sclerosis incidence. Contraception. 1993;47:161-8.
21. Thorogood M, Hannaford PC. The influence of oral contraceptives on the risk of multiple sclerosis. Br J Obstet Gynaecol 1998;105:1296-9.
22. POSER S, Raun N, Wikström J, Poser W. Pregnancy, oral contraceptives and multiple sclerosis. Acta Neurol Scand 1979;59:108-18.
23. Kupershmidt L, Amit T, Bar-Am O, Youdim MB, Blumenfeld Z. The neuroprotective effect of Activin A and B: Implication for neurodegenerative diseases. J Neurochem 2007;103:962-71.