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Review article

Contraceptive use among women with multiple sclerosis: a systematic review☆,☆☆

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Abstract

Background: Contraception is an important consideration for women with multiple sclerosis (MS); however, little is known about the possible effects of hormonal contraception on disease progression or other adverse outcomes (e.g., thrombosis, low bone mineral density).
Objective: To evaluate the evidence on the safety of contraceptive use among women with MS.
Search strategy: We searched the PubMed database for peer-reviewed articles published in any language from database inception through July 2015.
Selection criteria: We included studies that examined health outcomes among women diagnosed with MS initiating or continuing a contraceptive method. We excluded case reports and case series but included all other study designs.
Results: From 111 articles, we identified four studies (from 5 articles) that met our inclusion criteria. Evidence from one randomized controlled trial, two retrospective cohort studies, and one cross-sectional study suggests that use of combined oral contraceptives (COCs) or oral contraceptives (OCs) (type not specified) among women with MS does not worsen the clinical course of disease, defined as *disability level*, *disease severity or progression*, *relapse* or *number of new brain lesions on magnetic resonance imaging* (body of evidence grading Level I, fair to Level II-3, poor). No studies were identified that examined the safety of other contraceptive methods or examined other outcomes of interest (venous thromboembolism, changes in bone mineral density) related to contraceptive use among women with MS.
Conclusions: Limited evidence suggests that COC or OC use after MS onset does not worsen the clinical course of disease.
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Keywords: Multiple sclerosis; Contraception; Combined oral contraceptives; Oral contraceptives; Systematic review

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system in which the immune system attacks the myelin, disrupting communication between the brain and the rest of the body. Symptoms of MS vary widely over time and among individuals, depending on the amount of damage and which nerves are affected. Symptoms may include optic neuritis, sensory and gait disturbances, muscle weakness, tremor, spasticity, vertigo, bladder dysfunction and fatigue [1].

The course of MS has been categorized into several disease patterns based on disease activity and progression [2,3]. Clinically isolated syndrome (CIS) is the first clinical presentation of a disease compatible with MS that has yet to fulfill diagnostic criteria. Relapsing remitting MS (RRMS) is characterized by clearly defined relapses with no disease progression in between. Secondary progressive MS (SPMS) is characterized by an initial RRMS disease course followed by progression with or without acute relapses. The last disease pattern is primary progressive MS (PPMS), characterized by disease progression from onset with occasional

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plateaus or temporary minor improvements, with or without acute relapses. PPMS accounts for approximately 10–20% of cases at onset [4]. The nonrelapsing patterns are associated with greater neurological disability.

Although data are not available on the prevalence of MS among women of reproductive age in the United States, estimates suggest that 135 persons per 100,000 in the United States have MS [5], which translates to roughly 435,000 people [6]. As women are affected 2.4 times as often as men [7], we estimate that roughly 307,000 women in the United States have MS. Contraception is an important consideration for women with MS because the peak age of onset for women is during the childbearing years [8], and the disease does not impair fertility [9]. Further, since use of disease-modifying therapies to treat MS is generally not recommended for women seeking to achieve pregnancy and some are known teratogens [10], use of effective contraception is important to prevent unintended pregnancies among women using these treatments.

Most epidemiological evidence suggests no association between oral contraceptive (OC) use and risk of developing MS [11]; however, these data do not provide information on possible effects of hormonal contraception in women with MS, including disease progression or other adverse outcomes. MS patients have increased risk for venous thromboembolism (VTE) due to disability, immobility and autoinflammatory processes [12,13], which may be further increased with combined hormonal contraceptive use. MS patients may also have compromised bone health [14], so use of progestin-only injectables may be of concern. On the other hand, endogenous and exogenous hormonal exposures have been shown to stabilize MS [15,16]; thus, hormonal contraceptive use may positively affect the MS disease course.

The U.S. Centers for Disease Control and Prevention (CDC) publishes the U.S. Medical Eligibility Criteria for Contraceptive Use (US MEC) [17], which provides evidence-based guidance on the safety of contraceptive methods for women with certain characteristics or medical conditions. Currently, the US MEC does not include recommendations for contraceptive use by women with MS. As part of a process to update the US MEC, the objective of this systematic review was to evaluate the evidence on the safety of contraceptive use among women with MS.

2. Materials and methods

We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. Our key question was whether women of reproductive age with MS using a specific contraceptive method are at increased risk for adverse outcomes (e.g., relapse, disease progression, VTE, change in bone mineral density) compared with women using a different method or no method of contraception.

2.1. Literature search

We searched the PubMed database for peer-reviewed articles published in any language from database inception through June 2015 on the safety of using any contraceptive method among women with MS, using the following search strategy:

((((((((((contracept OR mirena) OR ((((“Norpregnanes”[Mesh] OR (“Contraceptive Agents”[Mesh] OR “Contraceptive Agents “[Pharmacological Action])) OR “Contraceptive Devices”[Mesh]) OR “Contraception” [Mesh])))) OR ((((((progest*)) OR ((((“Progestins”[Mesh] OR “Progesterone Congeners”[Mesh])) OR “Progesterone”[Mesh])))) AND (((contracept*) OR ((((“Norpregnanes”[Mesh] OR (“Contraceptive Agents”[Mesh] OR “Contraceptive Agents “[Pharmacological Action])) OR “Contraceptive Devices”[Mesh]) OR “Contraception” [Mesh])))))) OR (((((((((dmpa)) OR ((depo-provera))) OR ((norethisterone enanthate)))) OR ((“Medroxyprogesterone 17-Acetate”[Mesh])))) AND (((contracept*) OR ((((“Norpregnanes”[Mesh] OR (“Contraceptive Agents”[Mesh] OR “Contraceptive Agents “[Pharmacological Action])) OR “Contraceptive Devices”[Mesh]) OR “Contraception” [Mesh])))))) OR ((((iud)) OR ((“Intrauterine Devices” [Mesh])))) OR ((((emergency contraception)) OR ((“Contraception, Postcoital”[Mesh] OR “Contraceptive Agents”[Mesh])))) OR ((((nuvaring)) OR (((“Desogestrel”[Mesh] OR “Contraceptive Agents, Female”[Mesh]) OR “Contraceptive Devices, Female”[Mesh])))) OR (((((hormonal patch)) OR ((ortho evra))) OR (((“Norgestrel”[Mesh] OR “Contraceptive Devices, Female”[Mesh]) OR “Contraceptive Agents, Female”[Mesh])))))) AND (((“Multiple Sclerosis”[Mesh] OR “Multiple Sclerosis, Relapsing–Remitting”[Mesh] OR “Multiple Sclerosis, Chronic Progressive”[Mesh])) OR “multiple sclerosis”)*

In addition, we hand-searched reference lists from articles identified by the search and key review articles.

2.2. Selection criteria

We reviewed titles as well as abstracts to identify studies examining the safety of using any contraceptive method among women with MS. We included studies that examined health outcomes among women diagnosed with MS initiating or continuing a contraceptive method. We excluded case reports and case series but included all other study designs.

2.3. Study quality assessment and data synthesis

The evidence was summarized and systematically assessed using standard abstraction forms. The quality of each individual piece of evidence was assessed using the grading system developed by the United States Preventive Services Task Force [19]. We focused on several study factors when assessing quality, including study design, diagnostic criteria for MS, assessment of contraceptive use,