Multiple sclerosis, urinary tract infections and infertility: a comprehensive scoping review

Fatemeh Nezamzadeh[1], Koray Görkem Saçıntı[2,3], Aylin Esmailkhani[4], Özden Kargın[5], Mohammad Esmaeil Amini[6], Murat Sönmezer[5], Abed Zahedi Bialvaei[6]

[1]Islamic Azad University Faculty of Medicine, Tonekabon, Iran
[2]Department of Obstetrics and Gynecology, Ankara University Faculty of Medicine, Ankara, Türkiye
[3]Department of Public Health, Division of Epidemiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye
[4]Department of Microbiology, Tabriz University of Medical Sciences Faculty of Medicine, Tabriz, Iran
[5]Ankara University Faculty of Medicine, Ankara, Türkiye
[6]Microbial Biotechnology Research Center, Iran University of Medical Sciences, Tehran, Iran

Abstract

Multiple sclerosis (MS) is an autoimmune disease that involves the central nervous system. MS is prevalent among young adults and progressively destroys axons and myelin. Individuals with MS often experience complications, such as lower urinary tract dysfunction, urinary tract infections (UTIs) and sexual dysfunction. In young adults MS may cause sexual dysfunction and infertility, which worsens as the disease progresses. The available evidence from different studies (microbiological and clinical studies, retrieved from PubMed and Scopus databases) on possible microbial pathogens causing MS was reviewed. Lower urinary tract dysfunction, UTIs and sexual dysfunction were investigated in people with MS. Over the past two decades advances in MS treatment have significantly slowed disease progression and altered its natural history. However, UTI and sexual dysfunction continue to pose substantial challenges for affected patients. As there is a causal relationship between UTIs and corticosteroid use during outbreaks, awareness of essential complications of MS, such as UTIs and infertility, is crucial for prevention, early diagnosis, and adequate management. [J Turk Ger Gynecol Assoc. 2025; 26(2): 130-41]

Keywords: Multiple sclerosis, infertility, urinary tract infections, sexual dysfunction

Received: 3 August, 2024 **Accepted:** 23 December, 2024 **Publication Date:** 10 June, 2025

Introduction

Lower urinary tract and sexual dysfunction are common in individuals with neurological conditions, such as multiple sclerosis (MS) (1,2). The high prevalence of genital symptoms reflects the complex neural control of the lower urinary and genital tracts within the central and peripheral nervous systems (3). These issues significantly threaten quality of life and have gained increased attention among neurologists. The increased prevalence of these symptoms underlines the importance of evaluating the link between MS and related complications. Although, there is no consensus, numerous articles have shed light on the connection between MS, urinary tract infections (UTIs), and infertility.

Address for Correspondence: *Abed Zahedi Bialvaei*
e-mail: *abedzahedi@gmail.com* ***ORCID:*** *orcid.org/0000-0003-3564-9566*
DOI: *10.4274/jtgga.galenos.2024.2024-5-2*

Cite this article as: *Nezamzadeh F, Saçıntı KG, Esmailkhani A, Kargın Ö, Amini ME, Sönmezer M, Bialvaei AZ. Multiple sclerosis, urinary tract infections and infertility: a comprehensive scoping review. J Turk Ger Gynecol Assoc. 2025; 26(2): 130-41*

A higher prevalence of UTI is seen among patients with MS. This is primarily due to urinary dysfunction and impaired bladder evacuation. The severity of MS also seems to be a risk factor for UTI, which usually precedes MS relapse. UTI can also complicate disease progression and may even be the cause of severe outcomes. MS has been linked to a higher prevalence of sexual dysfunction, ranging in severity from pain to complete genital paresthesia and various other symptoms. These urinary symptoms may correlate with the spinal cord involvement of the disease. The complex relationship between sexual dysfunction and how it relates to the lower urinary tract and the gastrointestinal system is well understood and requires a multifaceted strategy to treat these symptoms.

Despite conflicting reports, some research has highlighted the increased prevalence of infertility in MS patients (4). Some articles further state that pregnancy may protect against MS and reduce disease symptoms (5). This is not surprising, as the change in sex hormone milieu during pregnancy is known to affect other autoimmune conditions, such as systemic lupus erythematosus, which worsens during pregnancy, and, rheumatoid arthritis, which improves during pregnancy and then relapses again after delivery.

In this paper, the issue of infertility from the perspective of MS will be discussed. This paper provides an overview of possible microbial pathogens that cause MS, an evaluation of individuals with MS who report UTI and infertility, and a comprehensive update on several recent advances that have revolutionized the treatment (Table 1). To achieve this aim, studies published within the last 20 years and retrieved from reputable databases, such as PubMed and Scopus, were reviewed and the findings synthesized.

An overview of multiple sclerosis

MS is a chronic neuroinflammatory disease characterized by demyelination and varying degrees of axonal loss. MS is reported to be the most common neurological disease, mainly affecting young women between the ages of 20 and 45 years (6), and it is approximately three times as likely to occur in women compared to men (7). The exact cause of MS is not known; however, genetic factors such as human leukocyte antigen (HLA) allotypes (e.g., HLA-DR2), environmental factors such as inadequate exposure to sunlight and decreased vitamin D (8,9), higher body mass index, smoking, and latent microbial infections that lead to myelin and axonal damage (10,11) have been implicated. When stimulants bind to myelin proteins, they trigger a complementary autoimmune response that causes oligodendrocyte destruction, neuronal injury, perivascular inflammation, and chemical alterations in the lipid composition of myelin (12). Lesions primarily occur in the white matter, optic nerves, spinal cord, and periventricular regions, leading to atrophic pillars with fibrosis. The characteristics that correlate with the location of each lesion are linked to the severity and clinical subtypes of the disease (13). The first clinical event in these cases can be optic neuritis, myelitis deficiency, or brain stem pattern (14). Increasing disease duration, higher degree of disability, and being a woman are independently associated with higher symptom levels as measured by the urogenital distress inventory (UDI-6). Participants with moderate disability had scores 11.6 points higher than participants with mild disability on the UDI-6, whereas participants with severe disability had scores 17.6 points significantly higher ($p<0.0001$) (15). In 70% of these cases, urinary symptoms are caused by functional and neurological deterioration (16). Moreover, studies have shown that more women with MS are diagnosed with infertility than women without MS (12).

Extensive research has focused on investigating and treating genitourinary problems in MS. Neurologists should address these conditions, especially since many of these problems can now be treated symptomatically. Appropriate and timely treatment can help prevent further complications and thus boost the general quality of life of individuals with MS.

Potential microbial pathogens causing multiple sclerosis

It has previously been proposed that infectious pathogens play a role in the pathophysiology of MS, leading to clinical manifestations of the disease in genetically susceptible individuals (8). However, despite decades of intense research, no particular pathogen has been proven to cause MS. This is due to the possibility that microbial infections may create autoreactive cells, and intermingling microorganisms are usually cleared by the time a clinical diagnosis is made. Moreover, MS patients and healthy people may produce antibodies or autoreactive T cells against particular infectious pathogens. The development of MS may also differ depending on the type of infectious agents identified suggesting that a deeper understanding of the entire genome of the microorganism may be necessary to understand the mechanisms at work. In addition, autoimmune responses can vary during the progression of the particular infection, as some microorganisms induce a strong autoimmune reaction. In contrast, in others, this autoimmune response is reduced by the production of regulatory cells (17). Furthermore, the diversity of the clinical subtypes of MS can be a confounding factor in associating infections with the causes of MS. For instance, infections may not directly initiate an autoimmune response but rather precipitate subclinical conditions of the autoimmune system, for example radiologically isolated syndrome, which later progress to clinical disease (18).

Table 1. The summary of most critical articles referred to in this query, along with the broad issue and the specific factor they investigated

Study (references)	Broad issue	Specific factor being examined	Population	Outcome	Statistical significance
Fingerman and Finkelstein (6)	MS demographics	Age parameters of MS	N/A	The most common neurological condition affecting adults between the ages of 20 and 45 is MS.	N/A
Fingerman and Finkelstein (6)	MS demographics	Gender parameters of MS	N/A	Women are three times more likely than men to be MS patients.	N/A
Munger et al. (9)	Risk factors for MS	Vitamin D	148 cases, 296 controls	For every 50 nmol/L rise in 25-hydroxyvitamin D levels in white people, the risk of MS decreased by 41%. For various races, both statistically significant and insignificant data have been presented.	p=0.04
Xu et al. (91)	Risk factors for MS	High BMI	952 cases vs. 743,596 controls	The risk of MS raised with each unit (kg/m^2) increase in BMI.	Hazard ratio and 95% confidence interval (CI): 1,034; 1,016-1,053
Antonovsky et al. (92)	Risk factors for MS	Smoking	241 cases vs. 964 controls	Before the age at onset, a significantly larger percentage of patients (in contrast with controls) smoked.	p=0.02
Ascherio and Munger (8)	Risk factors for MS	EBV infection	1,770 EBV + cases, 9 EBV - cases, 2,374 EBV + controls, 152 EBV - controls	Only EBV stands out as a predictable and significant risk factor among the infectious agents that have been suggested to be linked to MS.	p<0.000000001
Marrie et al. (15)	MS associated complications	Lower UTI	9,688 total responders to the questionnaire	According to a linear regression analysis, being a woman, having a more severe impairment, and having a more prolonged condition were all independently linked to having more symptoms as measured by the UDI-6. On the UDI-6, participants with moderate disabilities scored 11.6 points more than those with mild disabilities, and those with severe disabilities scored had 17.6 greater points.	p<0.0001
MacDonald et al. (89)	MS associated complications	Infections and MS	1,439 women with MS vs. 1,101,165 women as controls	An estimate for the cumulative incidence for infections during pregnancy is 57.7% and 43.4% for women who are not MS patients and for those who are, respectively. The most prevalent type of infections is found to be genitourinary infections.	95% CI: 1.16, 1.27

Table 1. Continued

Study (references)	Broad issue	Specific factor being examined	Population	Outcome	Statistical significance
Houtchens et al. (76)	MS associated complications	Infertility	96,937 women with MS vs. 96,937 women as controls	Compared to women without MS, a considerably higher percentage of women who are MS patients (8.5% vs. 8.1%) were diagnosed to be infertile.	p=0.0006
Houtchens et al. (76)	MS associated complications	Live birth rates	96,937 women with MS vs. 96,937 women as controls	Women with MS had a considerably reduced total live birth rate when contrasted with women without MS (5.0% vs. 7.0%).	p<0.0001
Fong et al. (79)	MS associated complications	Rates of cesarean sections in MS patients	1,185 MS births that were affected with MS vs. 4,424,049 total deliveries	The prevalence of cesarean deliveries was shown to be greater among pregnant women with MS.	p<0.001
Chen et al. (81)	MS associated complications	Rates of cesarean sections in MS patients	174 women with MS vs. 1,392 controls	MS patients were found to be more likely to undergo cesarean sections.	p=0.032
Jalkanen et al. (85)	MS associated complications	Need for artificial insemination	61 births from MS patients vs. 55,547 controls	Artificial insemination was more frequently required to initiate pregnancies among MS patients.	p=0.0009
Lamaita et al. (12)	MS associated hormonal alterations	AMH alterations	Meta-analysis of 16 articles	Smaller ovaries with fewer follicles and lower AMH levels were seen in patients with uncontrolled disease and also in those with active MS as well.	N/A
Thöne et al. (71)	MS associated hormonal alterations	AMH alterations	76 reproductive-age females with RRMS vs. 58 healthy controls	Women with relapsing remitting MS were found to have a considerably lower mean AMH level.	p<0.04
Nikseresht et al. (40)	MS associated hormonal alterations	UTI as a result of urinary problems that occur due to MS	7 MS patients	Individuals with UTIs had a considerably higher prevalence of urinary problems than individuals without UTIs (64.5% vs. 40%, respectively).	p=0.036
Grinsted et al. (70)	MS associated hormonal alterations	Prolactin, LH, FSH, total and free testosterone alterations	14 women with MS vs. 14 control women	Prolactin, LH, and FSH levels were considerably greater in MS patients.	p<0.05
Grinsted et al. (70)	MS associated hormonal alterations	Estrogen alterations	14 women with MS vs. 14 control women	The serum levels of oestrone sulphate was substantially lower in the MS patients.	p<0.01
Grinsted et al. (70)	MS associated hormonal alterations	Testosterone alterations in women	14 women with MS vs. 14 control women	Total and free testosterone concentrations were notably higher in MS patients.	p<0.01

Table 1. Continued

Study (references)	Broad issue	Specific factor being examined	Population	Outcome	Statistical significance
Falaschi et al. (73)	MS associated hormonal alterations	Testosterone alterations in women	76 women with MS vs. 50 control	According to a specific questionnaire, MS patients had a higher incidence of hyperandrogenism (greasy skin, acne, and hirsutism) when compared to controls. This finding was statistically significant.	p<0.05
Foster et al. (93)	MS associated hormonal alterations	Testosterone alterations in men	4 men with MS vs. lab references	Men who are multiple sclerosis patients had demonstrated reduced total testosterone levels.	p=0.002
Fong et al. (79)	MS associated risks	Risk of UTI in parturients with MS	1,185 MS births that were affected with MS vs. 4,424,049 total deliveries	UTI rates were observed to be more common in pregnant women with MS.	p=0.003
Jalkanen et al. (85)	MS associated risks	Risk of preterm delivery in MS patients	61 births from MS patients vs. 55,547 controls	MS patients did not pose a statistically significant risk of cesarean sections.	p=0.965
Jalkanen et al. (85)	MS associated risks	Risk of preterm delivery in MS patients	61 births from MS patients vs. 55,547 controls	MS patients did not pose a statistically significant risk of preterm deliveries.	p=0.800
Fong et al. (79)	MS associated risks	Risk of preterm delivery in MS patients	1,185 MS births that were affected with MS vs. 4,424,049 total deliveries	Unadjusted data for preterm delivery indicated a slightly higher risk in MS participants, however following statistical adjustment, this link was found to be non-significant.	p=0.007
Chen et al. (81)	MS associated risks	Risk of preterm delivery in MS patients	174 women with MS vs. 1,392 controls	Preterm birth rates were higher among mothers with MS.	p=0.001
Marrie et al. (52)	UTI associated complications	The prevalence of genitourinary sistem diseases as a cause for hospital admission	5,797 persons with MS vs. general population cohort of 28,769 persons	Diseases of the genitourinary system were the second most frequent cause of hospital admission in the MS population.	p<0.0001
Harding et al. (56)	UTI associated complications	The role of UTI in patient mortality	176 UTI-related MS patient deaths (8.2%) vs. 10,746 UTI related deaths irrespective of MS (1.4%)	Deaths attributed to MS were more likely to be caused by UTI compared to deaths without any reference to the disease.	p<0.002

MS: Multiple sclerosis, BMI: Body mass index, EBV: Epstein-Barr virus, UTI: Urinary tract infections, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, AMH: Anti-mullerian hormone, RRMS: Relapsing-remitting multiple sclerosis, UDI: Urogenital distress inventory, N/A: Not available

Despite this, pathogens linked to the emergence or exacerbation of MS includes bacteria, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, Herpesviruses (Epstein-Barr virus and Herpesvirus 6), enterotoxins produced by *Staphylococcus aureus* that act as superantigens, and human endogenous retrovirus families (19). In addition, *Acanthamoeba castellanii* protozoa and Candida fungal infections have also been considered (20). The results of studies conducted on human and animal models to investigate the relationship of these different pathogens with the occurrence and/or aggravation of MS, along with effective pathways such as molecular mimicry, epitope expansion, and bystander activation, have been discussed. However, infection with some parasites, including worms (*Hymenolepis nana*, *Schistosoma mansoni*, *Fasciola hepatica*, *Ascaris lumbricoides*, *Trichuris trichiura*, *Enterobius vermicularis*, *Strongyloides stercolaris*), appears to be associated with the occurrence or aggravation of MS (21).

Acute recurrences of MS are often triggered by upper respiratory tract infections (URTIs) or UTIs. Sibley et al. (22) were the first to define a two-week and a five-week risk before and after the onset of infection, during which the disease activity increases, likely due to an increase in the susceptibility to the infection (23). In considerable agreement with these findings, other investigators have demonstrated that disease aggravations during the high-risk period are more likely (24), and lead to prolonged relapses of increased severity (23).

Correale et al. (25) also studied whether UTIs had a relevance and showed a heightened risk of relapse during systemic infections. Furthermore, they demonstrated in transwell vulnerable cell co-cultures that myelin antigens induced an increase in antigen-specific T cell line proliferation during relapse, which possibly comes into being via vulnerable non-specific mechanisms. In addition to the activation of myelin-specific autoreactive T cells, other mechanisms have been considered to explain the observed association between MS and infections, such as molecular mimicry, antigen-based vulnerable cell activation, and direct microbial effects on the central nervous system (25,26).

Toll-like receptors (TLRs) are key factors in the human innate immune system. TLRs signal the production of inflammatory cytokines and interferons in response to stimulation by microbial epitopes, which then trigger additional adaptive immune responses (27). TLR2 and its heterodimeric partners, TLR1 and TLR6, are expressed on naive human regulatory T cells (Tregs) compromised in MS, potentially hindering their regulatory function (28). The processes behind how infections affect the clinical exacerbations of MS and the disease's progression are still poorly understood.

Urogenital and sexual dysfunction in multiple sclerosis patients

Genital dysfunction is a common problem affecting people of all ages, societies, and races (29). Although it is not yet fully defined, lower urinary tract dysfunction is a potential threat to the health of individuals and may lead to serious outcomes from UTIs. Urinary and sexual dysfunction can also compromise psychological and socio-economic wellbeing of individuals with MS (30). Both urine storage and excretion may be affected by MS, for which a functional assessment can only be made via urodynamic testing. Although estimates vary among studies, frequency depends on the stage of disease progression. Goldstein et al. (31) found that 2% of people with MS report having lower urinary tract dysfunction as their first symptom.

Neurogenic bladder disease probably affects virtually all individuals with advanced MS. Urodynamic abnormalities were detected in 52% of urologically asymptomatic patients with a relatively short mean disease duration of 5 years (32). As the neurological disease progresses, the treatment of bladder dysfunction becomes more complicated due to worsening detrusor overactivity, ineffective bladder evacuation, intermittent UTIs, spasticity, reduced mobility, and, sometimes, cognitive impairment (33).

Since upper urinary tract dysfunction is rare and preventable with well-timed ultrasound imaging, early-stage diagnosis in an MS center by a neurologist and a specialized nurse is recommended. The most frequent symptoms indicative of lower urinary tract dysfunction in MS are polyuria, urinary retention, urinary urgency, nocturia, and incontinence (34,35). A detailed history, urinalysis, and post-voiding residual urine determination by ultrasound provide the necessary data to treat infections, incontinence, and urgency. Treatment options include anticholinergics, bladder training, and intermittent catheterization. The need for a referral to a urologist can be considered in cases where first-line treatment has not provided adequate improvement. Treatment in end-stage MS has not yet been adequately studied, but in these cases, a suprapubic catheter is the favored technique for bladder drainage.

Urinary tract infections in multiple sclerosis patients

The frequency of UTI and bacteriuria in MS cases is high, with rates of 90% and 74%, respectively (36). This is largely due to urinary dysfunction, which can lead to increased hospitalization and nursing home admissions (36,37). Bladder evacuation in MS cases is closely related to UTI (38). Due to urinary issues, MS cases are prone to urinary tract colonization and, as a result, UTIs (39,40). Neurogenic bladder infection risk factors include increased urinary stasis, high bladder pressure, bladder stones,

and catheters (41). In addition, elderly age group, past antibiotic use, and the severity of MS are all risk factors for UTI (42,43). UTI often precedes MS relapse, and intermittent UTI is associated with acute exacerbations and neurological progression of the disease (36). Furthermore, it can be challenging to diagnose UTI in MS cases due to pre-existing urinary issues, which can result in misdiagnosis (40).

The most common symptoms of UTI in MS patients are urine retention, nocturia, urinary urgency, polyuria, and incontinence. Moreover, UTI in these patients can complicate the disease, cause additional damage, and even lead to severe neurological deterioration. In an extensive study of 458 (91.4%) subjects with MS who reported lower urinary tract symptoms, 130 (28.4%) reported intermittent UTI based on microbiological confirmation of bacteriuria and pyuria (44). It should be noted that UTI frequently occurs alongside symptoms such as increased bladder sensation, urine incontinence, increased frequency, urinary urgency, burning, dysuria, and/or lower urinary tract discomfort in people with MS (44). Urinary infections also increase hospitalization and mortality rates in this group. Therefore, MS cases with positive urinalysis or urinary symptoms should receive disease-modifying treatments and corticosteroid therapy.

In the MS population specifically, bacteria responsible for UTI were: *Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli*, beta-hemolytic *Streptococcus* B, and Coagulase-negative *Staphylococcus* (35,45,46). In a study of 146 cases with neurogenic bladder, Clark and Welk (47) examined the results of follow-up urine cultures from patients with at least two positive urine cultures in two years. Their findings showed that the most common organisms were *K. pneumoniae*, *P. aeruginosa*, and *E. coli*. According to other research, *E. coli* was isolated frequently (50%) in instances of neurogenic bladder, followed by *Acinetobacter* (15%), *P. aeruginosa* (15%), *E. faecalis* (6%), and mixed organism infections (41,48,49). Treatment of UTI should follow standard guidelines by determining the cause of infections and implementing preventative measures with intermittent infections, along with concurrent careful monitoring of bladder function and ultrasound (50,51).

Hospitalization and mortality rate from urinary tract infection in multiple sclerosis patients

In MS cases, UTIs are one of the top three most common reasons for hospitalization, accounting for 30-50% of hospitalizations (52). In a study of patients with neurogenic bladder, spinal cord injury, and MS, Manack et al. (53) discovered that 31% of cases had UTIs within a year of diagnosis, and 21% required hospitalization for UTIs. Furthermore, a link has been reported between a high "Extended Disability Status Scale" score and prolonged illness duration, which raises the risk of infection (54,55). UTIs have also been identified as a predictor of death in individuals with MS (43,54). Harding et al. (56) examined the causes of MS-related deaths in British Columbia, Canada, between 1986 and 2013 (56). They inspected mortality rates using the International Classification of Diseases and determined which conditions contributed the most to the death of MS cases. Compared to deaths not related to MS, those that were due to MS were more likely ($p<0.002$) to be caused by UTI. This underscores the importance of preventing and managing UTIs in individuals with MS to improve their overall health and reduce mortality risk.

Management of lower urinary tract symptoms

Urinalysis and symptoms should guide treatment in each group, whether in clinically stable cases or cases with relapsing MS. There is no evidence to suggest that antimicrobial treatment is clinically effective in cases of asymptomatic bacteriuria. The prevalence of drug-resistant bacteria may substantially increase due to treatment of asymptomatic bacteriuria. However, treatment is recommended in certain cases, such as pregnant women, patients presenting with intermittent acute UTI, before treatment of UTI, or in cases where immunosuppressive drugs are used. The activated immune response may be one possible reason of progressing disease and an otherwise stable situation worsening (57).

The use of corticosteroids is contraindicated in cases of UTI, as it prevents the patient from mounting an optimal immune response and increases the risk of progression into a systemic infection, which may become life-threatening due to complications (39,41). Steroid use can make infection control more challenging after starting the treatment regimen (58). If the patient has a UTI or bacteriuria, the current practice is to determine the presence of infection before starting treatment in acute relapse.

A case report by Tutuncu et al. (59) showed the association between MS exacerbations and UTIs. This study reported the development of severe dysarthria and diplopia alongside a new gadolinium-enhancing lesion preceded by the emergence of the disease. After treating the UTI, it was fully healed within two weeks. This can be achieved through careful history taking, bedside tests, and examination, including urine dipstick, a rapid and effective screening tool (60). This is useful in clinical situations where the use of steroid medication is essential to alleviate the symptoms associated with an acute relapse, thus minimizing short-term complications, which include both sensory or motor dysfunction of the patient.

When markers of infection are positive on a urine marker and the case is confirmed to have an acute relapse, it should be determined whether signs of systemic disease are present.

It is wise to use antibiotics to treat UTI and to use corticosteroids to reduce the recurrence of the patient's condition (39). This can promote lower levels of discomfort, greater satisfaction, less severity, and a shorter relapse period. To ensure safety, it is a priority to educate and advise the patient to call or return to the clinic if systemic symptoms, such as fever or convulsions occur (58).

Sexual dysfunction in multiple sclerosis patients

MS is linked to a higher prevalence of sexual dysfunction, regardless of gender. Men may experience dysfunction regarding erections and ejaculations. In contrast, women may experience decreased lubrication and genital hyper/hypo-sensitivity, which may even include complete anesthesia or hypoesthesia, and various types of pain (61). Most of these complications seem to be related to the involvement of the spinal cord in MS, typically associated with the lower extremities and urinary symptoms. As shown by magnetic resonance imaging in patients with relapsing-remitting multiple sclerosis, sexual dysfunction is also related to severe lesions in the pons (62). Clinical examination may not rule out neurogenic sexual dysfunction, but it can determine the scope of other MS-related deficits associated with sexual counseling, such as spasticity and loss of sensation.

Electrodiagnostic studies, including measurements of vibratory thresholds in the clitoris (63) and cortical evoked potentials of the dorsal clitoral nerve (64), imply that pudendal somatosensory input is essential for female orgasmic function, which may also be the case in early and mild MS. Depending on the clinical parameters of the analyzed samples and the follow-up time, sexual dysfunction occurs in 30% to 70% of cases (65). Among female patients with MS, the most common instances of sexual dysfunction are decreased libido (31-64%), decreased vaginal lubrication and sensation (33-52%), and anorgasmia (37-38%) (66). In men with MS, the most common instances of sexual dysfunction are decreased sexual desire (37-86%), erectile dysfunction (34-80%), decreased sensation (21-72%), ejaculatory dysfunction (34-61%), and difficulty reaching orgasm (29-64%) (67).

Bowel and bladder problems associated with MS can also affect sexual activity and interfere with intimate behavior and social relationships (68). Increased libido can also sometimes cause problems (69).

Studies show women with MS have reduced estrogen and higher follicle-stimulating hormone (FSH) and luteinizing hormone levels during the early follicular phase (70). Decreased ovarian reserve has been associated with higher FSH levels in the early follicular phase. Various different studies have reported an increased prevalence of hyperandrogenism and hyperprolactinemia in women with MS (55). In addition, reduced levels of anti-Mullerian hormone, a peptide hormone of the ovarian follicular pool and physiology, have been observed in women who have MS when contrasted with healthy women (71). Moreover, ovarian volume and antral follicle counts were decreased in MS patients using immunomodulating drugs (72). These alterations could explain why one of these studies demonstrated that there was a slight increase in the prevalence of oligo/amenorrhea in women with MS (16% in controls) (73). In men, decreased testosterone levels may affect sperm production, libido, and sexual function (74). However, good sperm production may be preserved despite abnormal testosterone levels (75).

Infertility in multiple sclerosis patients

Women with MS have been discouraged from getting pregnant for a long time due to worries about their ability to care for their children due to incapacity or fatigue (71). There is a significantly larger percentage of infertile women with MS than women without MS (8.5% vs. 8.1%; p=0.0006) (76). When stratified by age, the results showed that more women with MS between the ages of 18-34 years and 42 years and older had received a diagnosis of infertility when contrasted with women without MS (76). There is conflicting evidence about both the possibility of decreased fertility in MS patients and the impact of infertility treatment on the progression of MS. Likewise, it has been suggested that assisted reproductive technology increases the risk; however, there is insufficient evidence to confirm this claim (77).

Ashtari et al. (5) reported that MS has no effect on pregnancy outcomes, such as the number of miscarriages, ectopic pregnancies, stillbirths, and length of pregnancy, but it may also reduce the symptoms of the disease during the length of pregnancy. Thus, in their study, pregnancy had a protective role against MS. Despite the differences in male and female cases, overall, there is no conclusive evidence that women with MS experience fertility problems (4). Furthermore, infertility affects a large percentage of people who are of childbearing age, and thus MS may not always be the only cause. This issue should be discussed with MS patients, as some avoid pregnancy due to the fear of complications and lack of understanding regarding the use of medications in an appropriate safety class for pregnancy, and also the positive association between pregnancy and disease severity should be discussed. In addition, to ensure the greatest outcome for the mother and the fetus, it is important to counsel the patients regarding the most appropriate contraceptive methods, the best time to begin medical treatment, and the specific medication to use during pregnancy (12).

Perinatal outcomes in multiple sclerosis patients

As many pregnant women are MS patients (78-80), larger cohorts are expected to be studied to explore their risk for uncommon pregnancy complications. In some reviews, many (79-82), but not all (83-86), studies have reported higher rates of preterm delivery and Cesarean delivery among women with MS compared to women without MS. However, rarer complications, such as chorioamnionitis and postpartum hemorrhage, are not often considered (79). It is probable that women with MS have an increased risk of developing these complications due to a higher risk of prolonged labor and labor induction (83,86,87). Prior research investigating the likelihood of neonatal abnormalities in mothers with MS are generally in line in reporting an absence of increased risk, although sample sizes were limited (83,88). Moreover, many researchers have examined whether a more active disease had a correlation with increased risks of unfavorable pregnancy outcomes. The tendency for MS patients with milder disease to become pregnant contrasted with those who have comparatively more severe MS may ultimately lead to a lower risk of adverse pregnancy outcomes in women with MS. This may skew the data to demonstrate MS poses a lower-than-actual risk with regards to pregnancy outcomes. There is a critical knowledge gap in this area regarding the risks of adverse pregnancy outcomes in women with moderate to severe disabilities (86). According to one study, pregnant women with MS may be at a moderately increased risk of infection and premature delivery (89). Although the confidence intervals were broad and zero for all subtypes except genitourinary and respiratory infection subtypes, this study showed that women with MS had an increased risk of all infection subtypes except influenza.

Impact of multiple sclerosis treatment on infertility

In recent years, the treatment for MS has become more successful and has improved the quality of life, which has increased the willingness of parents to undergo successful infertility treatments. Therefore, couples should be managed in terms of the potential side effects of the medications used in the treatment of gonads, the impact of the disease on fertility, and the use of ovarian stimulation and its effect on MS. Published articles provide guidance on legal issues in situations where infertility treatments may adversely affect the progression of MS, as well as recommendations for how to treat infertility in MS patients. An interdisciplinary approach between neurologists and gynecologists is recommended to assess the risks and benefits of a particular procedure or treatment. For those who do not undergo MS infertility treatment due to MS-related medical conditions, they are advised to preserve gametes under the conditions prescribed by law (90).

The choice of treatment options for infertile couples with underlying neurological conditions depends on several factors. We need to determine whether the disease itself affects the reduction of ovarian reserve (DOR, a disorder that could result in infertility as the ovary loses its normal capacity for reproduction), and whether the medications used to treat the underlying disease are gonadotoxic. It is important to ensure that the underlying disease is not exacerbated by assisted reproductive techniques, and these procedures should be performed under optimal conditions. Any treatment of infertile couples with underlying conditions must be interdisciplinary and personalized, as the small number of these cases provides limited solid data in the literature on which we can base our decisions (90).

Conclusion

Neurological patients who report genitourinary symptoms require a comprehensive evaluation to plan a case-specific treatment approach. In addition, common URTIs, digestive tract, and genitourinary tract are also associated with MS exacerbations. Moreover, there seems to be a connection between the severity and course of the disease and various factors that may affect fertility. The limitations of this article are mainly due to the lack of research and consensus in certain topics, for example preterm delivery and the need for cesarean sections in pregnant women who have MS. Broader areas, such as fertility and how it is linked to the presence or severity of MS, has not been clearly shown in literature, although research suggest an association between the two. All in all, MS does not preclude the use of assisted reproductive technology in certain circumstances where it may be deemed necessary. Assisted reproductive technology does appear to be beneficial for conception in patients with MS, which is a supporting factor for the disease's association with infertility. Ultimately, MS should never be evaluated as an isolated neuropathy but rather be approached holistically. It may cause an extensive spectrum of complications, including infertility. Therefore, further research should be conducted to shed light on the relationships between MS and infertility, as well as with the latest techniques available for each stage or group of treatments used. Healthcare providers should always provide individualized care for their patients, especially regarding infertility, as it warrants additional investigation.

Footnotes

Author Contributions: *Surgical and Medical Practices: F.N., K.G.S., A.E., Ö.K., M.E.A., M.S., A.Z.B., Concept: F.N., K.G.S., A.E., Ö.K., M.E.A., M.S., A.Z.B., Design: F.N., K.G.S., A.E., Ö.K., M.E.A., M.S., A.Z.B., Data Collection or Processing: F.N., K.G.S., A.E.,*

Ö.K., M.E.A., M.S., A.Z.B., Analysis or Interpretation: F.N., K.G.S., A.E., Ö.K., M.E.A., M.S., A.Z.B., Literature Search: F.N., K.G.S., A.E., Ö.K., M.E.A., M.S., A.Z.B., Writing: F.N., K.G.S., A.E., Ö.K., M.E.A., M.S., A.Z.B.

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

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