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REVIEW ARTICLE

Assisted Reproductive Technology and Disease Management in Infertile Women with Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) predominantly affects women of fertile age. Various aspects of MS could impact on fertility, such as sexual dysfunction, endocrine alterations, autoimmune imbalances, and disease-modifying therapies (DMTs). The proportion of women with MS (wMS) requesting infertility management and assisted reproductive technology (ART) is increasing over time. In this review, we report on data regarding ART in wMS and address safety issues. We also discuss the clinical aspects to consider when planning a course of treatment for infertility, and provide updated recommendations to guide neurologists in the management of wMS undergoing ART, with the goal of reducing the risk of disease activation after this procedure. According to most studies, there is an increase in relapse rate and magnetic resonance imaging activity after ART. Therefore, to reduce the risk of relapse, ART should be considered in wMS with stable disease. In wMS, especially those with high disease activity, fertility issues should be discussed early as the choice of DMT, and fertility preservation strategies might be proposed in selected cases to ensure both disease control and a safe pregnancy. For patients with stable disease taking DMTs compatible with pregnancy, treatment should not be interrupted before ART. If the ongoing therapy is contraindicated in pregnancy, then it should be switched to a compatible therapy. Prior to beginning fertility treatments in wMS, it would be reasonable to assess vitamin D serum levels, thyroid function and its antibody serum levels; start folic acid supplementation; and ensure smoking and alcohol cessation, adequate sleep, and food hygiene. Cervico-vaginal swabs for Ureaplasma urealyticum, Mycoplasma hominis, and Chlamydia trachomatis, as well as serology for viral hepatitis, HIV, syphilis, and cytomegalovirus, should be performed. Steroids could be administered under specific indications. Although the available data do not clearly show a definite raised relapse risk associated with a specific ART protocol, it seems reasonably safe to prefer the use of gonadotropin-releasing hormone (GnRH) antagonists for ovarian stimulation. Close clinical and radiological monitoring is reasonably recommended, particularly after hormonal stimulation and in case of pregnancy failure.

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Key Points

The request for assisted reproductive technology (ART) in multiple sclerosis (MS) increases over time.

ART can potentially trigger disease activity in women with MS.

ART should ideally be initiated in women with stable MS.

Thorough periconceptional evaluation should be performed.

Gonadotropin-releasing hormone (GnRH) antagonists are reasonably preferred for ovarian stimulation.

1 Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease that affects young adults [1, 2], however, pediatric cases and late-onset cases after 50 years of age are also possible [3, 4]. The peak incidence is between 20 and 45 years, making it possible for MS to affect women in childbearing age [1, 2]. Despite up to one-third of women with MS (wMS) delivering a child after disease onset [5], it has been reported that MS considerably impacts reproductive choices, leading to the MS population having fewer children [6, 7] and delaying their first childbirth compared with the general population [8, 9].

The reason for increased childlessness in wMS may be due to maternity-related concerns about future disability, transmitting the disease, fear of a negative effect of pregnancy on the disease or a negative effect of MS on pregnancy outcome [8, 9], the use of disease-modifying therapy (DMT) not compatible with pregnancy, sexual dysfunction caused by MS, and, in some cases, infertility [10–12].

It is well known that most women have 12% of their follicle pool remaining at age 30 years, falling to 3% at age 40 years. Therefore, postponing maternity may raise the risk of infertility. Furthermore, in wMS, ovarian aging can occur as a result of immune suppressant chemotherapy that may be used to control high MS activity [13]. Whether MS itself may be associated with reduced fertility is still debated, as the limited number of studies conducted thus far have provided conflicting results [9, 14–18]. For instance, a register-based study from Denmark observed that wMS had a total fertility rate lower than non-MS women, without differences regarding the number of elective abortions, spontaneous abortions, or ectopic pregnancies after disease onset [6]. Additionally, a large study from the US confirmed these results, also showing that more women in the MS group than in the non-MS group were diagnosed with infertility, mainly between 18 and 34 years of age and > 42 years of age [9]. Various factors could impact fertility in wMS, such as sexual dysfunction, endocrine alterations, autoimmune imbalances [18], and DMTs [19].

A pilot study investigating the pituitary-ovary axis and ovarian reserve, including anti-Müllerian hormone (AMH) levels and ultrasound imaging of the ovaries, demonstrated that relapsing-remitting wMS with higher disease activity had significantly lower AMH levels, reduced total antral follicle count, and decreased ovarian volume than those with lower disease activity [12]. Therefore, women with higher disease activity, who might postpone pregnancy to first stabilize the disease, might also be at increased risk of reduced fertility. In this scenario, an increasing number of wMS are seeking pregnancy [9], reassured by the introduction of new DMTs that have changed the management of family planning for wMS [20]. Accordingly, the proportion of wMS requesting infertility management and assisted reproductive technology (ART) treatments is increasing over time. [21, 22]. Although available data show that the live birth rate (LBR) is not decreased in wMS undergoing ART, some relevant data are still missing in the literature. For example, it is uncertain whether ovarian stimulation is safe and which is the best ART protocol for wMS [7, 23]. Although the effect of ART on the immune system in wMS still needs clarification, some case reports [24–26] and small trials with different ART protocols [27–31] have shown an increase in MS activity after ART [32].

Recently, Bove et al. [33], pooling data from various studies examining the relapse rate after ART procedures, observed that the annualized relapse rate (ARR) was significantly higher in the 3 months following ART compared with the preceding 12 months. It is uncertain whether hormonal stimulation with gonadotropin-releasing hormone (GnRH) antagonists in wMS is less detrimental to disease activity compared with stimulation with GnRH agonists or vice versa. However, since it has been reported that the relapse rate after ART may be partly related to the procedure failure [29], it is conceivable that the increase in MS activity after ART may be triggered by the sudden decrease in estrogen levels occurring after the failure of ART, as it happens after abortion [34] or delivery in wMS with physiological pregnancy [35]. In this scenario, neurologists taking care of wMS will be increasingly asked by their patients about the possibility of undergoing ART and its effects on the disease.

The overall aims of this paper were to review the newer aspects of ART in wMS, discuss the clinical considerations when initiating therapy and planning a course of treatment for infertility, address safety issues, and update recommendations for reducing the risk of an increase in relapse rate after ART. These recommendations could guide clinicians in optimizing the management of wMS undergoing ART.

2 Literature Search Methodology

Five members of a multidisciplinary working group, involving neurologists, reproductive medicine specialists, and pharmacologists, all with an interest in MS, reviewed the literature and attended three web meetings to discuss the following topics:

- effect of sex hormones on the immune system;
- pharmacokinetics and pharmacodynamics of drugs used in ART protocols;
- ART plan;
- pharmacological interactions between DMTs for MS and drugs used for ART protocols;
- disease characteristics compatible with ART;
- DMT management in women undergoing ART;

- disease monitoring during ART.

The multidisciplinary working group involved four other people (one neurologist, two gynecologists, and one pharmacologist), all with experience in MS, to collaborate in the literature review. After reviewing the literature over a 12-month period ending in June 2022, they all discussed the above topics and finalized the recommendations about the management of wMS undergoing ART.

The literature search was conducted using the PubMed electronic database. The studies were identified using a combination of the following text words: 'Multiple Sclerosis' OR 'autoimmune disease' OR 'autoimmunity' OR 'chronic disease' OR 'demyelinating disease' AND 'fertility' OR 'infertility' OR 'IVF' OR 'in vitro fertilization' OR 'ART' OR 'assisted reproductive technology' OR 'assisted conception' OR 'reproduction' OR 'conception' OR 'gonadotrophins' OR 'GnRH agonist' OR 'GnRH antagonist' OR 'GnRH analogues' OR 'ovulation induction' OR 'family planning', from inception of the database to June 2022. A total of 2993 results were retrieved. The review of articles also included the abstracts of all the references retrieved from the search. Duplications were removed using Endnote online software, and manually. Only articles written or translated in English were considered for inclusion. Unpublished or non-peer-reviewed studies were not included. The review included all observational studies, case series and case reports, as well as reviews and expert opinions that evaluated the issue of reproduction in wMS, notably examining ART procedures in this population. At the end of the selection, 140 articles were included as references for the specific issues of the recommendations, and another 13 were added after the revision process, which prompted an update of the literature search until July 2023. After a preliminary web meeting aimed at establishing the literature search criteria and the tasks of each group member, and after having examined the literature, the panel of authors met twice via an online platform to discuss and elaborate on the following recommendations.

3 Effect of Sex Hormones on the Immune System

It is known that sex hormones have an immunological effect depending on serum levels. In particular, high serum levels of estrogens change the profile of the T-helper (Th) cells, shifting the Th1 (proinflammatory) immune response to the Th2 (with an anti-inflammatory effect) profile. Estrogens act as regulators of the immune responses through two nuclear estrogen receptors (ER)—Erα and Erβ. Acting on these receptors, high levels of estradiol have an anti-inflammatory action on astrocytes and microglia [32]. Other sex hormones also take part in the neuroinflammation and neurodegeneration processes. Progesterone has neuroprotective, promyelinating, and anti-inflammatory effects in the central nervous system (CNS) by stimulating oligodendrocyte maturation and myelin formation, decreasing the number of astrocytes, microglial cells, and inflammatory factors, such as interleukin (IL)-1, tumor necrosis factor, IL-6, inducible nitric oxide synthase and cyclooxygenase-2 [36].

4 Pharmacokinetics and Pharmacodynamics of Drugs Used in the Assisted Reproductive Technology (ART) Protocol

4.1 Pharmacokinetics and Pharmacodynamics of Gonadotropin Agonists

Gonadotropins are peptide hormones that regulate ovarian and testicular functions; they are essential for normal growth, sexual development, and reproduction. Human gonadotropins include follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are produced in the pituitary gland, and chorionic gonadotropin, which is produced by the placenta. All three gonadotropins are heterodimeric proteins made up of two peptide chains: the alpha chain is similar among all three proteins, while the beta chain is unique and determines the specificity of the receptor and the function of each hormone [37]. The gonads, testes, and ovaries are the primary target organs for LH and FSH. Gonadotropins interact with different cell types and generate multiple responses in target organs: LH stimulates the Leydig cells of the testes and theca cells of the ovaries to produce testosterone (and indirectly estradiol), while FSH stimulates the spermatogenic tissue of the testes and the cells of the granulosa of the ovarian follicles, as well as stimulating the production of estrogen by the ovaries [37].

Several gonadotropin analogs, which can be recombinant proteins or can be extracted from the urine of postmenopausal women and subsequently purified, are currently available. They are all approved to promote multiple follicular developments in women participating in ART programs (for details see Table 1).

4.1.1 Follicle-Stimulating Hormone (FSH) Preparations and Analogs

Follitropin alfa/beta/delta consist of recombinant FSH; they differ from each other in the degree of glycosylation due to the different cell lines in which they are produced. *Urofollitropin* is a highly purified urine-derived hormone, obtained from human post-menopausal gonadotropin (menotropin, hMG), with follicle-stimulating activity. *Corifollitropin alfa* is a fusion protein with no LH activity. A single injection of corifollitropin alfa can replace seven

daily injections of gonadotropin during the first week of ovarian stimulation, leading to similar pregnancy rates. The prolonged duration of FSH hormone activity is due to the addition of the carboxy-terminal peptide of the β subunit of human chorionic gonadotropin (hCG) to the β chain of human FSH [38].

4.1.2 Luteinizing Hormone (LH) Preparations and Analogs

Lutropin alfa is the first and only recombinant form of LH developed for the stimulation of follicular development. It stimulates theca cells to secrete androgens, which are used as substrate by the aromatase enzyme of the granulosa cells to produce estradiol. Follicular development is optimal if the drug is administered to women with hypogonadotropic hypogonadism and LH deficiency (< 1.2 IU/L) receiving subcutaneous lutropin alfa (dosage 0–225 IU/day) in combination with follitropin alfa [39]. No drug interactions with follitropin alfa have been observed when coadministered.

4.1.3 FSH and LH Preparations

Menotropin is also called human menopausal gonadotropin (hMG) and is obtained through purification processes starting from the urine of postmenopausal women. Menopause is indeed characterized by a hypergonadotropic state, in which FSH and LH levels are high. Menotropin-based preparations are used to stimulate follicular maturation as seen above. The recombinant process, used for the previous preparations, allows the production of pure FSH/LH that will not be 'contaminated' by other proteins possibly present after urinary extraction. However, no differences from a clinical point of view in the use of purified or recombinant FSH have been observed [40, 41] .

4.1.4 Human Chorionic Gonadotropin Preparations

hCG is a polypeptide hormone produced by the placenta after the implantation of the fertilized egg. Choriogonadotropin alfa, which mimics the activity of hCG, interacts with the LH receptors in the ovary, promoting the corpus luteum

Table 1 Pharmacokinetics of drugs used in ART protocols

Drugs	Route of administration	Absolute bioavailability	Terminal half-life	Steady-state volume of distribution [L]	Total clearance [L/h]	Excretion
FSH preparations and analogs						
Follitropin alfa	IV	66%	1 d	10	0.6	Urine
Follitropin beta	SC	77%	40 h	8	0.014	Urine
Follitropin delta	SC	64%	28 h	9	0.6	Urine
Urofollitropin	IM	70%	30-40 h	4.4	0.34	Urine
Choriofollitropin alfa	SC	58% (48–70%)	69 h (59 79 h)	9.2 (6.5–13.1)	0.13 (0.10–0.18)	Urine
LH preparations and analogs						
Lutropin alfa	SC	60%	8–21 h	10–14	1.8	Urine < 5%
FSH and LH preparations						
Menotropin	IM or SC	NA	30 h for subcutaneous, 27 h for intramuscular	NA	NA	Urine
Human chorionic gonadotropin preparations						
Choriogonadotropin alfa	SC	40%	30 h	6	0.2	Urine 10%
GnRH antagonists						
Ganirelix	SC	91%	13 h	76.5	2.4	75% feces, 22% urine
Cetrorelix	SC	85%	30 h	1.1 L/kg	0.7	Urine
GnRH analogs						
Buserelin	SC	70%	80–120 m	NA	NA	Urine
Triptorelin	SC	50%	2.8 ± 1.2 h	30–33	12.7	Urine
Leuprorelin	SC	94%	3 h	36	8.4	Urine < 5%
Goserelin	SC	100%	2–4 h	20.3	7.3	Urine

ART assisted reproductive technology, *NA* not available, *FSH* follicle-stimulating hormone, *IV* intravenous, *SC* subcutaneous, *IM* intramuscular, *LH* luteinizing hormone, *GnRH* gonadotropin-releasing hormone

and the production of progesterone necessary to maintain pregnancy and support the growth of the fetus. Injections of choriogonadotropin alfa mimic the LH surge necessary for ovulation and are used in female infertility therapy in ART protocols [37]. The metabolism is comparable with the endogenous hCG.

4.2 Pharmacokinetics and Pharmacodynamics of Gonadotropin-Releasing Hormone (GnRH) Antagonists

GnRH antagonists competitively bind to GnRH receptor sites, inhibiting the stimulation and release of gonadotropins from the pituitary gland. In ART protocols, they are used to prevent premature ovulation; they do not induce the initial flare-up effect and the response is highly dose-dependent [42]. Serum levels of FSH and LH decrease within a few hours after the administration of the GnRH antagonist.

The drugs currently approved for controlled ovarian hyperstimulation, i.e. the process through which multiple follicular growth is obtained with the abovementioned protocols, are Cetrorelix and Ganirelix, which mainly differ from each other in their half-life (Table 1). GnRH antagonists are not widely used compared with the analogs due to lower pregnancy rates [43].

4.3 Pharmacokinetics and Pharmacodynamics of GnRH Analogs

GnRH analogs are drugs acting on GnRH receptors. Following receptor activation, these drugs initially induce an increase in the release of LH (flare-up), but after repeated dose administrations, they induce a reduction of LH release due to receptor downregulation [44]. The drugs currently available on the market (triptorelin, buserelin, leuprorelin, goserelin) are mainly depot formulations (Table 1).

5 ART Plan

5.1 Preconceptional Care

Infertility is a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse [45]. According to the American College of Obstetrics and Gynecology, since fertility decreases with age, women older than 35 years of age should seek consultation and eventually start fertility treatments after 6 months of failed attempts to conceive [46]. Regarding the issue of reduced fertility in wMS, data on ovarian reserve are still conflicting [47]; however, like women in the general population, wMS may seek a fertility evaluation earlier than the 12 months of unprotected sexual intercourse period, especially if older than 35 years of age. wMS seeking pregnancy and undergoing ART treatments should be advised about smoking and alcohol cessation [48, 49], intake of folic acid [50, 51], sleep hygiene [52, 53], and a balanced diet [54–56].

The importance of vitamin D is widely acknowledged either in relation to immune system regulation [57, 58], MS activity [59, 60], or fertility [61]. The role of vitamin D in pregnant wMS is still debated as some studies did not find any association between vitamin D levels and the risk of post-partum relapse [62, 63], while others reported vitamin D deficiency in pregnant wMS and its supplementation reduced the relapse rate during pregnancy and within 6 months after delivery [64, 65].

Moreover, vitamin D deficiency has been associated with worse ART outcomes [66–68].

Considering the above-mentioned evidence, and also that a debate is still open on the possible role of vitamin D levels during pregnancy and the risk of MS in the offspring [69, 70], it is reasonable to evaluate vitamin D levels before conception and eventually prescribe supplementation to reach normal and stable values before starting the ART procedures [68, 71, 72].

Thyroid function is of fundamental importance not only for fetal development and pregnancy outcomes [73–76] but also to improve ART outcomes [77, 78]. It has been shown that the prevalence of thyroid disease is increased in the MS population compared with the general population [79, 80], with autoimmune thyroiditis being the most frequent [81, 82], and also in relation to MS treatments [83–85]. Interestingly, serum vitamin D levels are also significantly lower in people with autoimmune thyroid diseases [86]. Therefore, the evaluation of thyroid function and antibody levels should be performed, and dysregulation should be corrected to improve ART outcomes [87, 88].

Another important issue is peri-implantation glucocorticoid administration for ART cycles. Corticosteroids are the most used treatment in cases of acute MS relapses [89] and are also administered in cases of repeated in vitro fertilization (IVF) failure and recurrent miscarriage, as well as in women affected by autoimmune disorders or with positive autoantibodies, to improve pregnancy rates, sometimes also in co-treatment with aspirin, but with discordant results [75, 90–92].

Nørgård et al. [93] performed a systematic review to assess the efficacy of ART treatments in a variety of chronic diseases, the majority of which were autoimmune and/or inflammatory conditions (including MS). They observed that the use of steroids did not significantly increase the odds of ART outcomes. Currently, there is no clear evidence in favor of the administration of glucocorticoids in ART [23, 93, 94]. Hence, the evaluation of the usefulness of steroids before ART treatments should be done on a case-by-case basis.

In addition, infectious screenings (cervico-vaginal swabs for Ureaplasma urealyticum, Mycoplasma hominis and Chlamydia Trachomatis, as well as serology for viral hepatitis, HIV, syphilis, cytomegalovirus, and others) should be performed, taking into consideration the impact of infections on IVF outcomes [95] and the fact that wMS treated with specific DMTs could be more susceptible to infections [96].

Recommendations wMS older than 35 years of age might ask for fertility evaluation after 6 months of failed attempts to conceive. Prior to beginning fertility treatments in wMS, it would be reasonable to assess vitamin D serum levels, thyroid function and its antibody serum levels, as well as to start folic acid supplementation and ensure smoking and alcohol cessation, adequate sleep and food hygiene. Cervico-vaginal swabs for Ureaplasma urealyticum, Mycoplasma hominis and Chlamydia Trachomatis, as well as serology for viral hepatitis, HIV, syphilis, and cytomegalovirus have to be performed. Steroids could be administered under specific indications.

5.2 Ovarian Stimulation and LH Suppression

Ovarian stimulation consists of the administration of gonadotropins to induce multiple ovarian follicle growth, starting from the second day of the menstrual cycle (standard start) or in any phase when there is an urge to start therapies that are not compatible with fertility (random start, used in fertility preservation cycles). In addition, suppression of LH peak is requested to avoid spontaneous ovulations, which is achieved through the addition of GnRH agonist or antagonists [97]. Currently, there are no randomized controlled trials comparing the effects of different protocols for controlled ovarian stimulation (COS) in wMS. The only available evidence comes from small retrospective case series and cohort studies (Table 2) performed in the last decades. The first cases were reported by Laplaud et al. [29, 98] (6 wMS who had undergone 10 ART cycles). They observed that the relapse rate in the 3 months after IVF was significantly increased (in 5/6 wMS) and that none of the patients treated with GnRH antagonists for LH suppression had a relapse compared with those treated with GnRH agonists. Limitations of this study were the small sample size, the retrospective approach, and the absence of a control group.

Hellwig et al. performed two studies, the first with six patients who had undergone 14 ART cycles [27], and the second with 23 patients who had undergone 78 hormonal stimulations [28]; These authors found that none of the GnRH agonists or antagonists were associated with an increased ARR. Moreover, they did not confirm the findings of Laplaud et al. [29, 98] in relation to the increased risk associated with GnRH agonists, but agreed on the overall increased risk of ARR after ART treatments. Furthermore, they noticed that the frequency of the treatments did not influence the ARR. The studies by Laplaud et al. [99] and Hellwig et al. [27, 28] both suffered potential recall bias since patient recruitment was based either on neurologists/gynecologists being aware of the study or on advertisement. Moreover, the number and dates of MS relapses were provided through a questionnaire administered to patients [31]. Later, Michel et al. [31] performed a French multicenter study that included 32 wMS who had undergone 70 IVF treatments—48 using GnRH agonists and 19 using GnRH antagonists (for three IVF procedures, the type of drug used could not be retrieved). This study confirmed both the increased risk of relapse rate during the 3-month period post-ART and the increased risk in the case of the GnRH agonist protocol. No increased relapse rate in wMS treated with GnRH antagonists was detected. In addition, in their study, failure of the IVF treatment was associated with an increased risk of relapse. Limitations of that study were the small sample size, the retrospective approach, the absence of a control group, and selection bias (neurologists might have unintentionally enrolled more active patients).

In 16 wMS receiving 26 ART cycles with GnRH agonists and recombinant FSH, Correale et al. [30] showed a sevenfold increased risk of new exacerbations and ninefold increased risk of MRI activity in the 3 months after ART. These authors did not find any association with the IVF outcome, but reinforced the idea that the risk of relapse was enhanced by multiple IVF cycles. Worsening was associated with a higher number of cells producing IL-8, IL-12, interferon (IFN)-γ, and transforming growth factor receptor (TGF)-β, as well as increased vascular endothelial growth factor (VEGF) production by CD4+ T cells and chemokine (C–X–C motif) ligand (CXCL-12) plasma levels (all GnRH-mediated effects), and increased anti-myelin oligodendrocyte glycoprotein (MOG) antibody titers, B-cell activating factor and anti-apoptotic B-cell molecule Bcl-2 levels (effects mediated by a rise in 17-β estradiol production associated with ART). Of note, all patients were treated with GnRH agonists. Limitations of that study were the absence of blinding of clinical and radiological assessments and the small sample size (although the authors chose the self-controlled case series as a statistically efficient model to overcome this limitation).

Torkildsen et al. [25] reported a case of relapse during ART, notably after 3 days of gonadotropin treatment, i.e. before the use of either GnRH agonists or antagonists, for which the IVF attempt was immediately stopped.

Ladwig et al. [26] observed two cases of MS onset immediately after IVF procedures, with clinical diagnosis and radiological confirmation. It is noteworthy that both patients experiencing multiple IVF failures (two and four attempts, respectively); one patient was treated with GnRH antagonists and the other was treated with GnRH agonists. Similarly, Sakurai et al. [99] described a case of a woman

Table 2 Main studies on assisted reproductive technology in women with multiple sclerosis

Study	Country/year of publication	Study design	Sample size/ART cycle	Main results		Other results	Limitations
				RR in the 3 months after ART			
				GnRH agonist	GnRH antagonist		
Laplaud et al. [98]	France/2007	R	6/10	Increased	Not increased	Not reported	NR Potential recall bias[a]
Hellwig et al. [27]	Germany/2008	R	6/14	Increased	Increased	Not reported	Small sample size Retrospective approach
Hellwig et al. [28]	Germany/2009	R and P	23/78	Increased	Increased	RR after ART increased independently of the interval between the stimulations	Potential recall bias[a]
Michel et al. [31]	France/2012	R	32/70	Increased	Not increased	RR increased in the case of failure of ART	Small sample size Retrospective approach Memory bias[a] Absence of a control group
Correale et al. [30]	Argentina/2012	P	16/26	Increased	Not included in this study	Ninefold increase in the risk of MRI activity Increased RR was associated with a higher number of cells producing IL-8, IL-12, IFNc, TGFβ, VEGF, CXCL-12 plasma levels, anti-MOG antibody titers, BAFF and Bcl-2 levels	Small sample size Absence of blinding of clinical and radiological assessments
Bove et al. [33]	USA/2020	R, PA, and M	Boston cohort 12/22[a] Pooled analysis, 164 ART cycle	Not increased Increased	Not increased Increased		Observational study Absence of a control group Absence of assessment of emotional stress ART related
Mainguy et al. [101]	France/2022	R	225/338	Not increased	Not increased[a]	Lower RR after ART among wMS taking DMTs	Risks of selection Absence of date of effective use of MS and ART drugs Underestimated number of relapses in pregnant wMS

Table 2 (continued)

Study	Country/year of publication	Study design	Sample size/ART cycle	Main results		Other results	Limitations
				RR in the 3 months after ART			
				GnRH agonist	GnRH antagonist		
Graham et al. [102]	USA/2023	R	65/124	Not increased	Not increased	RR increased in cases with two or more stimulations DMT during COS was associated with a lower RR	Retrospective approach Possible data loss[a] Site-based limitations[a]

ART assisted reproductive technology, *R* retrospective, *P* prospective, *PA* pooled analysis, *M* meta-analysis, *RR* relapse rate, *GnRH* gonadotropin-releasing hormones, *NR* not reported in the paper, *MS* multiple sclerosis, *MRI* magnetic resonance imaging, *IL* interleukin, *TGF* transforming growth factor, *IFN* interferon, *CXCL* chemokine (C-X-C motif) ligand, *Bcl-2* B-cell lymphoma-2, *VEGF* vascular endothelial growth factor, *MOG* myelin oligodendrocyte glycoprotein, *BAFF* B-cell activating factor, *wMS* women with multiple sclerosis, *DMTs* disease-modifying therapies, *COS* controlled ovarian stimulation

[a]See text for details

affected by uterine fibroids and atypical bleeding, which was treated with GnRH agonists, and who experienced neurologic symptoms due to MS shortly after a few administrations. In a small case series, Shimizu et al. [100] noticed that the only patient who experienced a relapse after ART had already had a relapse shortly before the treatment and was also the only patient to suffer from a miscarriage after ART.

Jølving et al. [23] performed a very large register-based study (2267 embryo transfers in wMS and 200,684 in women without MS) exploring the reproductive outcomes of wMS after ART treatments, and showed that there was no difference in LBRs or in biochemical and clinical pregnancy rates after adjusting for confounders such as age, comorbidity, type of ART treatment, and cause of infertility. Jølving et al. also explored the role of pretreatment with steroids without finding significant differences. Limitations of that study were the absence of data regarding disease activity, type of DMT, Expanded Disability Status Scale (EDSS), reason for prescribing corticosteroids, and their dosage. Bove et al. [33] carried out a pooled analysis of the most important case series published thus far, including the abovementioned studies from France [31], Germany [28] and Argentina [30], and added an unpublished cohort from Boston. Interestingly, data from the Boston cohort (12 wMS receiving 22 ART cycles) showed no difference in ARR after ART compared with the ARR before ART, even when stratified by ART protocol and outcome. In this regard, noticeable data came from the MS treatment; in fact, MS patients were treated with DMTs until shortly before starting ART treatments. This would reflect the advances in the knowledge of DMT profiles of teratogenicity, showing more safety, and the related tendency to continue DMTs closely before such medical procedures to reduce the risk of relapses. However, pooling the data (a total of 164 ART cycles), it emerged that the ARR increased in the 3 months after ART compared with the 12 months before, and this significance is maintained after stratifying for parity, ART protocol, time off MS treatment, and ART outcome (pregnancy/no pregnancy) and adjusting for age, disease duration, and repeated observations. Moreover, the ARR was increased comparing the 3 months after ART with the 3 months before ART. In such a period, the ARR was also linked to ART failure compared with ART success, and to GnRH agonist protocols compared with GnRH antagonist protocols. Limitations of that study were its observational nature, absence of a control group, and assessment of emotional stress related to ART.

In a French study conducted on 225 wMS receiving 338 ART cycles, Mainguy et al. [101] confirmed no increase in the risk of relapse in the 3 months after ART. Notably, this study found a decreased ARR after IVF with the use of GnRH agonists and in IVF failure subgroups, but the authors concluded that it was probably due to a high ARR before IVF. In addition, this study showed a lower ARR after ART

among wMS who remained on DMTs until IVF, compared with untreated wMS. A limitation of that study was the absence of dates regarding the real start time of DMTs and the use of ART drugs. Moreover, since the relapses were identified considering MS-related hospital admissions and corticosteroid therapy, the use of a lower dosage of corticosteroids during pregnancy may have been responsible for an underestimation of the number of relapses in pregnant wMS. However, the authors concluded that despite this limitation, the results were not questionable because the number of pregnant wMS was less than half, and, above all, they conducted subgroup analyses, considering IVF successes (pregnant women) and failures separately.

In a multicenter study of 65 wMS undergoing 124 ART cycles, Graham et al. [102] confirmed that the ARR did not increase after ART and showed no difference between the use of GnRH agonists and antagonists. Additionally, the authors observed that the relapse risk increased in cases with two or more stimulations, while the use of DMT during COS was associated with a lower relapse rate in the 3 months after ART. A limitation of that study was its retrospective nature, which may have introduced recall bias for relapses, and the limited details regarding ART procedures. Site-based limitations were also possible, such as the timing of DMT suspension and ART protocol.

Considering the results of the aforementioned studies regarding the number of COSs and the increased ARR risk after ART, as well as the recommendations of the National Institute for Health and Care Excellence [103], a maximum of three full cycles of IVF are suggested. Based on the effects of sex hormones on the immune system, it is hard to understand why ART is potentially associated with disease activity in MS. It could be that flare-ups and drops in estrogen levels, during and at the end of COS, result in a detrimental effect on the immune system, as might happen after ART failure. Indeed, in case of failure, the abrupt decrease in estrogen levels might contribute to a sudden shift of the immune system from an anti-inflammatory profile to a proinflammatory profile.

Recommendations Current data do not clearly show a definite raised relapse risk associated with a specific ART protocol, but according to the evidence, it seems reasonably safe to prefer the antagonist protocol. A maximum of three ovarian stimulation cycles is suggested. No information could be drawn regarding types and doses of gonadotropins.

5.3 Adjuvant Therapies

The goal of COS is to induce the simultaneous growth of antral follicles, as many as there are in both ovaries at the time of the ART procedure [97]. As a collateral event, growing follicles produce estrogens (estradiol, in detail) and their serum levels increase dramatically in a short period of approximately 15 days at most [97]. However, there are conditions in which the ovaries could respond suboptimally to gonadotropins.

Therefore, sometimes ART protocols can be modified by adding other medications to gonadotropins, to increase the sensitivity of the ovary or the pituitary gland. In this regard, selective estrogen-receptor modulators, such as clomiphene citrate (CC), and aromatase inhibitors, such as letrozole, have been observed to not differ from GnRH agonist- or antagonist-alone protocols with respect to their effects on LBRs or pregnancy rates, either in the general population of women undergoing IVF treatment or in women who were poor responders [104]. CC has both estrogenic and anti-estrogenic properties; it can increase gonadotropin secretion by blocking the estrogen-negative feedback to the hypothalamic-pituitary axis and also the sensitivity of the granulosa to the gonadotropins themselves [105].

There is very scarce evidence regarding the use of CC in the subset of wMS asking for ART treatments. Laplaud et al. [29, 98] described the use of CC in addition to the antagonist protocol in two patients who did not experience relapses post-ART. In a case-control study, Houtchens et al. [7] explored whether these oral medications yielded different LBRs in wMS compared with healthy women, and found similar results.

Ashtari et al. [106] revealed that 10.6% of their sample had used infertility medications, with CC being used by 60% of the sample.

Nonetheless, the aromatase inhibitors work by determining a downregulation in the production of estrogens by inhibiting the cytochrome P450 [107].

Letrozole is a non-steroidal, highly selective oral aromatase inhibitor that can reversibly bind to the rate-limiting enzyme P450 aromatase in the estrogen biosynthesis pathway and inhibit the conversion of testosterone to estradiol and androstenedione to estrone [108]. The downregulated estrogen increases the secretion of pituitary FSH as feedback to stimulate ovulation. Nowadays, letrozole has been extensively used to induce ovulation in anovulatory infertility patients and to increase follicles for ovulatory women. Furthermore, letrozole is used as an adjunct for intrauterine insemination [109] and IVF/intracytoplasmic sperm injection cycles [110]. Letrozole is also used for fertility preservation in women with estrogen-sensitive cancers. Recent studies demonstrated that in women with hormone receptor-positive breast cancer undergoing COS with letrozole for fertility preservation, the cancer recurrence risk is not increased compared with women not undergoing COS [111, 112]. Moreover, other studies showed the effectiveness of letrozole in endometrium preparation for frozen-thawed embryo transfer [113, 114]. Moreover, this inhibition does not interfere with follicle growth or maturation, but only

with estrogen production. Some studies argued that the addition of letrozole during COS could negatively impact oocyte retrieval, but a recent meta-analysis observed significant differences neither in the number of collected mature oocytes nor in other cycle parameters [115]. Historically, letrozole was studied for ovulation induction in women affected by anovulatory infertility [116], and for COS in polycystic ovary patients to reduce the risk of ovarian hyperstimulation syndrome (OHSS) [114]. OHSS is characterized by massive enlargement of the ovaries, even after the oocyte pick-up and third space liquids' seizure, with possible ascites, pelvic or abdominal pain, hemoconcentration and thromboembolic risks, and can become a life-threatening condition, the pathophysiology of which is not yet fully understood [117, 118]. Estrogens and polycystic ovaries are considered as the main predisposing factors, the exogenous or endogenous hCG is the trigger agent, and the VEGF is the effector [119].

In fact, a reduced level of estrogens during ovarian stimulation has been observed when patients have been co-treated with letrozole [120].

Similar to MS, another autoimmune disease, systemic lupus erythematosus (SLE), has been observed to be exacerbated by ART treatments [121] and increased estrogen levels. Therefore, letrozole has also been proposed in SLE patients to reduce estrogen levels and to diminish the risk of disease flare-ups and thromboembolic events [122]. Graham et al. [102] described 10 wMS who underwent 14 cycles of oral ovulation induction, 6 with letrozole and 8 with CC. Only one wMS had one relapse within the 3-month post ovulation induction, however this patient was not receiving DMT. Data on the use of letrozole during ART in wMS are still limited in order to draw conclusions.

Recommendations There are scanty data on the use of adjuvant therapy to modulate the hypothalamic-pituitary axis for infertility treatments in wMS, not directly relating these drugs to the risk of MS relapse. Therefore, their use should be considered according to patient-specific infertility issues.

5.4 Ovulation Induction, Embryo Transfer, and Luteal-Phase Support

When at least two to three growing follicles reach 17–18 mm in diameter, ovulation triggering is performed to induce oocyte maturation [123]. This can be done with GnRH agonists or hCG. After 35–36 h from triggering, oocyte retrieval is carried out through a surgical procedure of transvaginal ultrasound-guided aspiration of the ovarian follicles [124]. Mature oocytes are then inseminated with the partner's sperm. This step can be achieved in vitro by placing the oocyte and spermatozoa together in a plate with a suitable culture medium, and allowing the spermatozoa to penetrate the oocyte in a natural way, or manually by embryologists (the so-called ICSI [intra-cytoplasmic sperm injection]). Afterwards, fertilization can be observed from the following day. Embryo transfer can be performed on day 3, at the cleavage stage embryo, or day 5, at the blastocyst stage [125]. Moreover, embryo transfer can be done with fresh or frozen embryos. When the embryo is frozen, the endometrium must be prepared to receive the embryo and allow it to implant. This step can be achieved with estrogen supplementation plus progesterone, or on a natural menstrual cycle, taking advantage of the spontaneous growth of a follicle and its related corpus luteum after ovulation. Finally, the embryo is transferred into the uterine cavity through a sterile catheter entering from the cervix [126].

The number of embryos to transfer has long been debated among fertility specialists. Currently, the practice of a single embryo transfer is gaining more and more diffusion to reduce the risk of multiple pregnancies [127]. During ART, the choice of LH suppression protocol also influences the ovulation triggering before the oocyte pick-up. In other words, if the GnRH agonist protocol is applied, it is not possible to use GnRH agonists for triggering and hCG must be administered. The latter is considered the gold standard in fresh transfer cycles and also for its role in the luteal-phase support. Conversely, GnRH agonists are preferred for triggering in GnRH antagonist protocols to reduce the risk of OHSS, when there is cycle segmentation followed by frozen-thawed embryo transfer (FET) [128]. Thus far, in wMS, no studies have evaluated the direct role of this choice, either on the relapse risk or ART outcomes. Jølving et al. [23] were the only authors who considered the proportion of FET among wMS undergoing ART treatments, reporting it as similar to non-MS women and with similar results in terms of ART outcomes.

Support of the luteal phase after embryo transfer has only been reported by Correale et al. [30] (using vaginal progesterone) and Hellwig et al. [27, 28] (using progesterone but not specifying the route of administration), but without precise information on doses and timing of administration.

Graham et al. [102] did not observe any increase in the relapse rate after COS followed by fresh and single embryo transfer.

Brzosko et al. [129], conducted a study on 29 wMS receiving 76 stimulations: 15.79% of stimulations used intrauterine insemination, 21.05% used IVF, 31.58% used ICSI, and 30.26% used intercourse. In four of five wMS (80%) relapsing after ART, the methods used for fertilization were IVF/ICSI. However, these data do not provide exhaustive information about the association between the type of transfer and MS clinical course.

Recommendations A limited number of studies have examined the role of different protocols for ovulation triggering, timing of embryo transfer and luteal phase support

to release evidence-based recommendations. Single embryo transfer is advised. Decisions should be guided by patient-specific infertility issues.

5.5 Fertility Preservation

Cavalla et al. [18] were the first to theorize the application of fertility preservation procedures in wMS. The rationale behind their proposal was related to the possible damage that ovaries could undergo when patients are treated with cytotoxic medications, reducing the pool of follicles and therefore reproductive chances. In addition, the evidence from studies evaluating ovarian reserve showed that more aggressive forms of MS could be associated with reduced AMH levels [47]. Thereby, the option of fertility preservation should be seriously considered by MS experts managing wMS of reproductive age. Strategies for fertility preservation not only encompass COS with mature oocyte cryopreservation but also ovarian tissue cryopreservation [130] and immature oocyte cryopreservation with in vitro maturation (IVM). The cryopreservation of mature oocytes requires hormonal treatments that, as mentioned above, carry the risk of MS relapses, while the other two strategies could be considered less hazardous. IVM has already been applied to two wMS eager for offspring, to which neurologists advised against GnRH analogs [131]. Therefore, Gulekli et al. [132] proposed MS as an indication for IVM, considering that an unstimulated cycle could be a very useful alternative for infertile wMS.

Recommendations The issue of infertility in wMS is still an open debate and therefore fertility preservation on a large scale is not recommended. However, in selected cases, after fertility evaluation, the pros and cons of fertility preservation strategies should be discussed with the patient. IVM could not only be a useful fertility preservation strategy but also a feasible alternative for women at higher risk of MS relapse who wish to attempt pregnancy through ART.

6 Pharmacological Interactions Between Disease-Modifying Therapies for Multiple Sclerosis and Drugs Used For ART Protocols

Due to the potential additional effects on heart rate, treatment SP1 modulators [133] with siponimod/ozanimod/fingolimod/ponesimod should generally not be initiated in patients who are concomitantly treated with QT interval-prolonging drugs with known arrhythmogenic properties, such as GnRH agonists (e.g., goserelin, buserelin, leuprorelin, triptorelin) [134]. If concomitant use of the two classes of drugs is considered, a cardiologist should be consulted in advance.

Recommendations Concomitant use of SP1 modulators and GnRH agonists should be avoided.

7 Disease Characteristics Compatible with ART

Consistent findings in wMS getting pregnant have naturally shown that among the preconception disease characteristics associated with a higher probability of inflammatory reactivation in the post-partum epoch, there is uncontrolled disease in the year preconception [135–137], preconception DMT exposure [135], and higher EDSS at conception [136]. This knowledge has been incorporated into preconceptional counseling, optimizing pregnancy planning and improving women's safety.

In the case of wMS undergoing ART, it can be assumed that post-partum relapses are predicted by the same risk factors as natural pregnancies. Nevertheless, in this population, it would be critical to identify the clinical characteristics predicting periprocedural relapses to optimize the timing of the procedure and minimize the risks. The available evidence suggests that a higher relapse count in the 3 months after ART seems to have a linear relationship, with a higher relapse rate in the previous 12 months [33]. Hence, ART should ideally be planned in wMS with stable disease.

Recommendations Although limited data are available in wMS conceiving through ART, prior to the procedure clinical and radiological monitoring of the disease should be obtained to timely plan ART and minimize the risk of periprocedural and post-partum relapses. Ideally, ART should be performed in wMS during the remission phase.

8 DMT Management in Women Undergoing ART

The use of DMTs among women of childbearing age has rapidly evolved during the past decade, increasing from a minimum monthly prevalence of 49.3% in 2011 to a maximum of 58.7% in 2019, according to a recent study conducted in the United States [138]. Therefore, it has been a matter of debate of how to manage DMTs in wMS seeking pregnancy. In the past, discontinuation of DMTs was usually recommended before pregnancy, with a washout period based on the mechanism of action and the pharmacokinetics of each DMT.

The recommendation of suspending DMTs in women with stable disease was motivated by the lack of data on the safety of fetal exposure to DMTs, although this was in contrast to the common behavior to continue treating patients who respond to treatment.

Based on accumulating evidence, these days suspension of DMTs due to pregnancy planning is no longer considered safe as it may increase the risk of relapses in the timeframe between interruption and pregnancy, during pregnancy, and post-partum [139], particularly in women treated with sequestering drugs such as fingolimod [102, 140] or natalizumab (NTZ) [102, 141]. Drug safety during pregnancy is influenced by the molecular size: the placental barrier can be easily crossed by small molecules (mostly oral medications) at any time point, but not by larger molecules (e.g. injectables or monoclonal antibodies) [142]. Therefore, S1P receptor modulators and teriflunomide are contraindicated during pregnancy [142]. The use of glatiramer acetate (GA) or IFN-β is allowed during pregnancy, and current guidelines recommend considering maintaining natalizumab until conception and during pregnancy in selected cases after full discussion with wMS [143, 144]. The newest evidence also supports the safe use of dimethyl fumarate until conception [145]. Anti-CD20 monoclonal antibodies still have restrictive pregnancy labels in both the EU and the US, despite reassuring safety data for use closer to pregnancy. In a recent work, based on the available data, the authors suggest targeting the last dose of anti-CD20 therapies shortly before pregnancy, but ideally not during pregnancy itself [142].

Limited evidence is available regarding the management of DMTs for wMS who require ART. Bove et al. [33] showed that in wMS with no treatment before ART, or suspending DMTs >3 months before, there was a significant increase in ARR after ART, which was not detected in women suspending DMTs < 3 months before ART. Such effect is likely explained by the additional risk due to the combination of DMT washout and hormonal stimulation.

Mainguy et al. [101] showed a lower ARR after ART among wMS who remained on DMTs until IVF, compared with untreated wMS. Graham et al. [102] confirmed that the use of DMT during COS was associated with a lower relapse rate in the 3 months after ART.

Furthermore, Brzosko et al. [129] and Range et al. [146] confirmed that the relapse risk after ART was lower in wMS who continued DMT. In the study by Brzosko et al. [129], wMS (followed in the German MS and family planning registry) continued DMT in most stimulations (59.2%). Only five relapses were registered after ART. Four of five wMS (80%) who had relapses after ART had stopped DMT prior to ART. Limitations of this study could be the small sample size and the retrospective approach.

Range et al. [146] conducted a prospective (for 18.15% of the sample), retrospective (for 81.85% of the sample) study in 91 wMS who had undergone 270 stimulations; 68.90% of wMS continued DMT during ART. Only 5.91% of wMS receiving DMT during ART had relapses, compared with 16.67% of wMS not receiving DMT during ART ($p = 0.009$), with no statistically significant difference between those who got pregnant and those who did not ($p = 0.6519$).

The main concern regarding continuing DMTs until ART consisted of the fear of adverse outcomes of the procedure due to exposure to treatments. A recent study [23] analyzing a large dataset extracted by the nationwide Danish health registries showed that wMS have no statistically significant reduced chance of a live birth compared with healthy women receiving ART. Detailed information regarding the DMTs used by these women was not available but such results are reassuring considering the high number of included cases.

Nevertheless, a clear relationship between DMT exposure and reduction of fertility and/or increased risk of adverse ART outcomes has not been established, nor is it expected considering pregnancy outcomes in the general population of wMS. In the case of naturally conceived pregnancies, exposure to GA [147], IFN [148], or natalizumab [149] does not increase the risk of spontaneous miscarriage during the first trimester of pregnancy.

Indeed, a matter of debate is whether wMS should be preventatively switched from modest to higher-efficacy therapies before ART, based on the consideration that ovarian stimulation might trigger MS relapses. However, no studies have investigated the risk/benefit of this management strategy, which might be proposed to women with unfavorable prognostic factors.

On the other side, a de-escalation strategy is unsafe and is associated with a higher risk of relapse [150]. Furthermore, the potential additional effect of prolonging the QT interval exerted by SP1 modulators and GnRH agonists should be considered if administered simultaneously.

Recommendations Considering the increased risk of MS relapse due to suspension of DMTs and the expected lack of any impact on ART outcomes, it is not advisable to interrupt treatments before ART in wMS. wMS treated with DMTs not compatible with pregnancy, or with GnRH agonists, should be switched to compatible treatments before ART. The continuation of GA and IFNs during ART pregnancy should be decided on an individual basis; the choice of maintaining natalizumab throughout pregnancy should consider the individual risk/benefit ratio, but it could be recommended. The available data are reassuring in the case of anti-CD20 therapies administered shortly before pregnancy, but ideally not during pregnancy itself.

9 Disease Monitoring During ART

Although this is an emerging need considering the potential increase of clinical and radiological relapses in wMS after fertility treatment, no specific monitoring protocols have been put in place to monitor disease activity during ART. Reasonably, close neurological follow-up should be

maintained during ART, particularly after hormonal stimulation, to rapidly identify wMS developing disease activation.

In addition, clinical and radiological re-baselining is needed after pregnancy failure, as abortion may induce inflammatory rebound both in natural [34] and ART pregnancies [31].

Recommendations Standardized protocols for MS monitoring during ART have not been established. However, close clinical and radiological monitoring is reasonably recommended, particularly after hormonal stimulation and in case of pregnancy failure.

10 Discussion

After a thorough literature search and multidisciplinary meetings, nine recommendations have been released regarding each step of the ART treatments and the management of infertility in wMS, from the preconceptional period to the embryo transfer.

The multidisciplinary approach [151] allowed full consideration of the various aspects (endocrinological, immunological, pharmacological, neurological, and purely reproductive) of the simultaneous management of MS and ART in infertile wMS.

Formal clinical practice guidelines would require a different approach with class A, level 1 evidence that is lacking on this topic. Instead, the task of the group was to address key issues (following the available scientific evidence) relevant to treatment optimization (either for controlling disease activity or for ART procedures) in wMS willing to undergo ART.

The pathophysiology of the increased relapse rate in wMS after the ART procedure is still not fully understood. It is reasonably safe to refer infertile wMS to ART procedures whenever the disease is stable, both for the risk of relapse in women with uncontrolled disease before ART [33] and for the evidence that the ovarian reserve could be negatively modulated (or definitively reduced) in wMS with active disease [11, 12].

Likely, a conceivable strategy to reduce the relapse risk associated with ART might be the use of adjuvant therapies such as aromatase inhibitors (i.e., letrozole) [as has been done in the model of fertility preservation in patients with hormone-sensitive tumors, or in autoimmune diseases such as SLE]. In fact, reduction of the circulating levels of estrogens under administration of aromatase inhibitors could produce smaller flare-ups and drops during and at the end of ovarian stimulation, probably resulting in a less detrimental effect on the immune system, with the consequence of reducing the post-ART relapse rate.

Furthermore, mild stimulation ART protocols, embryo freezing, or oocyte cryopreservation could be taken into consideration in selected cases where pregnancy is not yet expected but would be planned in the future (for personal reasons or medical conditions) while under DMT for MS and careful monitoring. Indeed, the issue of hormonal drop after ovarian stimulation and oocyte retrieval not followed by a fresh embryo transfer could mimic a miscarriage; in these cases, continuous MS therapy during the ART protocol and the possible addition of adjuvant therapy might help wMS to safely reduce the time to pregnancy [152, 153], performing the fresh embryo transfer in a following phase.

11 Conclusions

The recommendations provided here are intended to help neurologists and reproductive medicine specialists in safely and successfully managing their wMS seeking ART treatments. We suggest that ART should be preferably considered in wMS during stabilized phases of the disease, to reduce the risk of relapse after ART.

In wMS, it is not advisable to interrupt DMTs before ART, but wMS treated with DMTs not compatible with pregnancy should be switched to compatible treatments before ART [151]. If this possibility is not practicable, suspension of the DMT should be carried out considering clinical and radiological features and the type of ongoing treatment, suspending it, if possible, < 3 months before ART. This timing is established to reduce the risk of relapses, considering that no treatment before ART or suspending DMTs > 3 months before significantly increases the risk of relapse after ART.

We recommend multidisciplinary counseling before ART and multidisciplinary follow-up during and after ART, in the case of both childbirth and abortion. We strongly recommend tight cooperation between neurologists and reproductive medicine specialists in the management of wMS during ART. Furthermore, we suggest close monitoring mostly after hormonal stimulation (particularly in the first 3 months) and in the case of ART failure.

It is worth considering that most studies about ART in wMS are retrospective and with small sample sizes (see Table 2); information regarding the association between MS clinical course and the use of adjuvant therapies, luteal-phase support, and type of embryo transfer is lacking.

Since, in the last years, the ART protocols and the therapeutic approach to wMS seeking pregnancy have consistently changed, studies regarding the impact of ART on MS, also taking into account the new DMTs and the different therapeutic approaches to wMS with a desire for pregnancy, are needed.

Further studies on larger cohorts of wMS undergoing ART, or matching MS registries and registries of women who have undergone ART, are strongly awaited. In

particular, it is necessary to evaluate the risk of relapse associated with GnRH agonist and antagonist treatment, and to elucidate the impact of adjuvant therapies on ART outcome and on relapses to identify the best and safest ART protocol in wMS.

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