



REVIEW

Assisted Reproductive Techniques in Multiple Sclerosis: Recommendations from an Expert Panel

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ABSTRACT

Introduction: Multiple sclerosis (MS) is mainly diagnosed in women of reproductive age. However, there is a paucity of guidelines jointly prepared by neurologists and gynaecologists on managing women with MS and the desire for motherhood. Therefore, in this review we propose recommendations for such cases, with an particular focus on those requiring assisted reproductive techniques (ART).

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Methods: A group of seven MS experts (4 neurologists and 3 gynaecologists) came together for three discussion sessions to achieve consensus.

Results: The recommendations reported here focus on the importance of early preconception counselling, the management of disease-modifying therapies before and during ART procedures, important considerations for women with MS regarding ART (intrauterine insemination, in vitro fertilisation and oocyte cryopreservation) and the paramount relevance of multidisciplinary units to manage these patients.

Conclusions: Early preconception consultations are essential to individualising pregnancy

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management in women with MS, and an early, well-planned, spontaneous pregnancy should be the aim whenever possible. The management of women with MS and the desire for motherhood by multidisciplinary units is warranted to ensure appropriate guidance through the entire pregnancy.

Keywords: Assisted reproductive technology; GnRH antagonists; Multiple sclerosis; Oocyte cryopreservation; Preconception counselling

Key Summary Points

Since age is the main factor affecting a woman's fertility, an early preconception consultation is crucial.

In terms of multiple sclerosis (MS) treatment, if clinically indicated, interferon beta and glatiramer acetate could be considered throughout pregnancy and natalizumab until the third trimester.

Gonadotropin-releasing hormone antagonists are used in ovarian stimulation procedures for in vitro fertilisation to avoid risks.

Oocyte cryopreservation is an alternative assisted reproductive technique for young women recently diagnosed with MS who will have to delay their desire for motherhood.

The management of women with MS and maternal desire by multidisciplinary units is warranted to guide them appropriately through their pregnancy.

However, MS does not impair women's or men's fertility [2], and more than 40% of women with MS have become pregnant after receiving a MS diagnosis [3, 4]. MS also does not affect the course of the pregnancy nor is it associated with obstetric pathologies [5–7], unlike other autoimmune diseases, such as autoimmune hepatitis [8] or thyroid diseases [9]. Therefore, pregnancy is not discouraged in women with MS, although careful management of the each woman's condition before, during and after pregnancy is advised [10–12].

Women with MS need to wait for a period of stable disease and low radiological activity before attempting to conceive [7]. Consequently, these patients are often constrained to delay their desire for motherhood and may, therefore, be older than their healthy counterparts when ready to become pregnant [13, 14]. This reality renders women with MS more likely to require assisted reproductive techniques (ART) than the general population [15], but the risk-to-benefit ratio of pregnancy should be assessed individually. Also, the monitoring requirements of these patients, together with the inherent complexity of pregnancy, prompt a multidisciplinary approach to managing women with MS and maternal desire. Unfortunately, there are no guidelines or recommendations for managing these patients from a multidisciplinary gynaecology and neurology perspective.

The aim of this review was to put forward recommendations from a panel of neurologists and gynaecologists on managing people with MS and parenthood desire. In this context, we have reviewed the process in detail, from preconception counselling to in vitro fertilisation (IVF) and oocyte cryopreservation (OC). We also suggest approaches for implementing and improving multidisciplinary units to manage these patients.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune neurologic disease of the central nervous system that negatively impacts the patient's quality of life. MS is mainly diagnosed in women in their 30s—that is, women of reproductive age [1].

METHODS

A group of seven experts, coordinated by the first author (CO-G), including four neurologists who are experts in MS and three gynaecologists specialised in ART, met for three discussion

sessions to establish recommendations regarding ART in patients with MS. Before starting the consensus sessions, an update on the topic of interest from the neurological and gynaecological point-of-view, respectively, was given. In the first two preparatory sessions, key questions on infertility and ART in MS were formulated and discussed. The topics addressed were the importance of age in fertility, the risks of ART in MS, the optimal time of MS stability before undergoing ART and seeking pregnancy, the management of disease-modifying therapies (DMT) in patients undergoing ART, the ovarian stimulation procedure in women with MS, the waiting time for natural conception and the recommended age to request ART and age limits for oocyte or embryo cryopreservation. The consensus was established in a third virtual session. For each key issue, a recommendation was accepted if unanimous agreement was achieved. The information collected during the three sessions served as the basis for the writing of this article, in which all authors participated.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

OVARIAN CYCLE OVERVIEW

During the first days of the menstrual cycle (follicular phase), the growth of ovarian follicles is stimulated by the increasing concentration of follicle-stimulating hormone (FSH) [16]. Usually all but one follicle will stop growing, and the dominant follicle will continue to mature in the ovary. At the same time, oestradiol levels suppress the production of luteinising hormone (LH) and FSH from the anterior pituitary gland, the so-called negative feedback loop. At a certain point, the increase of in the plasma levels of these hormones stimulate a surge of LH (positive feedback) that leads to ovulation; this event is mandatory for the oocyte to achieve the first meiotic division. Then, the mature ovum is released into the fallopian tube. In the second part of the ovarian cycle (i.e. luteal phase), FSH and LH induce the transformation of the remaining parts of the follicle into the corpus

luteum, which produces progesterone, oestradiol and various types of peptides, including other signalling molecules. Both progesterone and oestradiol downregulate FSH and LH production, which leads to corpus luteum atrophy. If no fertilisation occurs, progesterone triggers menstruation and the next menstrual cycle begins [16]. However, in the case of fertilisation, the newly formed syncytiotrophoblast (and, later on, the placenta) produces human chorionic gonadotropin (hCG)—a hormone with a similar mechanism of action to LH but with a longer half-life—that allows the corpus luteum to survive.

The proper functioning of the corpus luteum is determinant for the appropriate development of gestation during the first 7–9 weeks of pregnancy. The corpus luteum produces progesterone in large quantities until approximately the 10th week of pregnancy, at which time the placenta takes the lead in progesterone synthesis. Oestrogen levels also increase gradually during gestation; the production of oestrone and oestradiol is increased by 100-fold and that of oestriol by 1000-fold [17].

RECOMMENDATIONS

Preconception Counselling

Multiple sclerosis is an incurable disease that entails an inherent degree of hardship, forcing those with the disease to be constantly challenged with accepting and coping with the new reality driven by their illness. Therefore, before initiating any steps towards pregnancy, specialists must ensure that the person with MS has accepted the disease [18]. Acceptance can be defined as the awareness of the need to adapt to a chronic illness while being willing to accept its unpredictable and uncontrollable nature [19]. However, in women with MS, as in the general population, age is the main factor affecting pregnancy rates [20], although other factors do play a critical role, such as ovarian reserve (estimated by plasma levels of anti-Müllerian hormone and/or antral follicle count by transvaginal ultrasound), body mass index and smoking [21]. Importantly, the DMT

chosen to manage MS must be appropriate to the desire of the patient for parenthood over the short or long term [10–12]. Therefore, shared decision-making, including family planning, is fundamental [22].

Early preconception counselling is paramount to inform and evaluate all parameters that could affect pregnancy. For example, the Spanish Society of Gynaecology recommends a preconception consultation for all women with the desire for motherhood [23]. The partner of the patient with MS, especially men, should also attend informative preconception consultations to rule out potential issues for both of them. During this consultation, the most important factor regarding fertility, which is the woman's age, should be emphasised [24], and subfertility factors could be identified. Notably, the DMT should be assessed, especially if a switch of DMT, or a washout period, is necessary before conception. Current recommendations from regulatory agencies include avoiding pregnancy during treatment and, depending on the DMT, maintaining a 2- to 6-month washout period before conception [25–27]. Finally, in women with MS, an evaluation of cervical pathologies through cytology tests should be undertaken since some DMT, in particular those with an immunosuppressing mechanism, such as mitoxantrone, azathioprine and alemtuzumab, have been associated with a potential risk of cervical dysplasia (Table 1) [28, 29].

Multiple Sclerosis and ART

Time frames should be individualised according to disease activity and gestation prognosis. However, a natural approach to becoming pregnant is generally recommended for a period of 6–12 months in women aged > 35 years and for 1 year in those aged < 35 years. This time frame would allow these women to shorten the time without treatment or with a suboptimal DMT [30]. Ideally, people with MS should begin the ART process with the lowest possible number of symptomatic treatments and at the minimum effective dose. Beyond their effects on pregnancy [31], DMT do not seem to hamper ART processes, whether stimulation,

fertilisation or implantation. Regarding natural pregnancies, DMT should be withdrawn according to their prescribing information, an individual risk-to-benefit assessment before pregnancy and/or after a positive pregnancy test result (neither during stimulation nor before implantation). Nonetheless, and based on post-marketing experience, some DMT can be considered during pregnancy if clinically indicated: interferon beta and glatiramer acetate throughout pregnancy, and natalizumab up to the third trimester, provided that their benefits to the patient outweigh their risks to the foetus (Table 1) [32, 33]. Despite data on pregnancy in women with MS exposed to antiCD20 being currently limited, taking into account the pharmacokinetics of these DMT, their low risk for placental transfer during the first trimester and the reassuring post-marketing clinical experience, they could also be considered in women with high-activity MS on a case-by-case basis [34].

In Vitro Fertilisation

The efficiency of ART techniques, mainly intrauterine insemination (IUI) and IVF, should be considered on an individual patient and/or couple basis, albeit IVF is economically more costly than IUI but has a higher live birth rate (LBR) per cycle [35]. A subclass of IVF, intracytoplasmic sperm injection (ICSI), is the most widely used fertility technique in developed countries [36]. In addition, a single embryo transfer in IVF-ICSI could avoid the risk associated with multiple pregnancies [37, 38]. Multiple pregnancy is the most frequent and serious iatrogenic complication in ART procedures [39], entailing not only obstetric risks for the mother (e.g. hypertension, preeclampsia, preterm labour) that should be avoided in women with pre-existing pathologies, but also risks for the foetus (e.g. preterm delivery, congenital malformations, cerebral palsy) [40]. Therefore, although the criteria for choosing one ART over the other are not different in women with MS compared to the general population, in this context the older age of women with MS and the importance of these women avoiding

Table 1 Summary of recommendations for the management of people with multiple sclerosis and the desire for parenthood*Preconception counselling*

- Wait until the patient has accepted her/his disease
- Early consultation in women of child-bearing age is advised
- Emphasise that women's age is the most important factor affecting fertility
- Other subfertility factors can be identified at this point
- Therefore, both partners should attend the consultation and be examined
- Patients should be informed of all available options to conceive
- The DMT should be assessed, especially if it requires a washout period
- Cervical pathologies should be evaluated
- Shared decision-making is fundamental

In vitro fertilisation

- Women < 35 years old should try to conceive naturally for 1 year
- Women > 35 years old should try to conceive naturally for 6–12 months
- Patients should begin the IVF process with the lowest possible number of symptomatic treatments and at the minimum effective dose
- DMT should be withdrawn according to prescribing information, as for natural pregnancies
- Single embryo transfer in IVF-ICSI is advised in people with MS to avoid multiple pregnancy risks
- Hormones used for ovarian stimulation should be individualised
- Ovarian stimulation treatments should be adjusted to avoid the risk of ovarian hyperstimulation syndrome
- The maximum number of stimulations recommended is three
- The concept of cumulative live birth rates should be clearly explained to patients
- For men with MS, only if DMT is proven to affect sperm quality, a DMT switch could be justified to obtain a sperm sample
- In cases of sexual dysfunction, electroejaculation or testicular biopsy can be used

Oocyte cryopreservation

- Take into account that early pregnancy is always more cost-effective than OC
- Oocytes or embryos can be cryopreserved
- First, the age at which OC is undertaken is the most critical factor
- Second, good to moderate ovarian reserve is required for OC
- The maximum number of stimulations recommended is three
- Women with MS can benefit from OC if they need to delay motherhood for one or more years and fulfil the abovementioned criteria

Table 1 continued*Multidisciplinary units*

- Early family planning is vital for the patient to remain without her DMT for the shortest possible time
- Age is also considered a risk factor regarding DMT use
- Multidisciplinary units are recommended to manage cases of people with MS and parenthood desire
- The communication between all specialists forming these units must be excellent
- The ethical implications of pregnancy and child-rearing in people with MS should be discussed within these multidisciplinary care units

DMT Disease-modifying therapy (therapies), *ICSI* Intracytoplasmic sperm injection, *IVF* in vitro fertilisation, *MS* multiple sclerosis, *OC* oocyte cryopreservation

multiple pregnancies are the main reasons why IVF-ICSI is the most used ART in this patient group. Most ovarian stimulations in IVF are currently performed with gonadotropin-releasing hormone (GnRH) antagonists, which are considered to be safer than GnRH agonists, to prevent an uncontrolled LH surge and ovulation [16, 41, 42]. No conclusive evidence is yet available on the effect of ovarian stimulation on disease activity or the relapse risk in people with MS, but in a recent study [43], the largest to date, which analysed 338 IVF procedures in 225 women, no increase in MS activity after ART cycles was observed. However, this study assessed relapses through healthcare registries, and milder ones may not have been included. Discrepancies between older [44, 45] and more recent studies may be explained, at least in part, by recent substantial changes in the treatment of MS, as preconception stabilisation of the disease has been strongly recommended in recent decades. In this context, Mainguy et al. observed a lower relapse rate before and after IVF in women who remained receiving DMT until IVF [43]. In addition, the switch from GnRH agonists to GnRH antagonists in ovarian stimulation protocols may also have reduced inflammatory activity in women with MS undergoing ART. Finally, the observed relapses after an unsuccessful IVF cycle may likely be due to discontinuation of DMT before the procedure, a sudden increase in hormone levels during ART and/or the effect these hormones may have on the activity of immune cells [16, 46].

The whole IVF-ICSI process in women with MS does not differ from that in the general population and consists of four steps: (1) preliminary consultations; (2) ovarian stimulation and ovulation induction; (3) oocyte retrieval and IVF; and (4) endometrium preparation and embryo transfer [47]. The patient's parameters, such as age, ovarian reserve and pre-existing diseases, all of which will determine the doses of hormones required, are analysed in informative preliminary consultations [48]. In the following step, ovaries are stimulated with a combination of hormones (such as synthetic FSH, LH and GnRH antagonists); this combination should be tailored to each individual patient, driven by clinical experience [48, 49]. Although the paucity of guidelines on ART proves the lack of general consensus on many technical aspects, the current National Institute for Health and Care Excellence (NICE) guidelines recommend a limit of three full cycles of IVF [50], which has also been demonstrated in real clinical practice [51]. Likewise, the ideal number of oocytes retrieved, albeit still debated, ranges from 10 to 15 [52]. Importantly, in patients with a pre-existing pathology, such as MS, the risk of developing ovarian hyperstimulation syndrome should be minimised [53]. This can be achieved by using a GnRH agonist instead of hCG in the ovulation induction step and by deferring embryo transfer (cryopreservation or transfer in following cycles). In summary, the risk-to-benefit ratio of ovarian stimulation should be carefully assessed in people with MS. The IVF-

ICSI process continues with ovulation induction with hCG, a GnRH agonist or both, which also induces the final oocyte maturation [47]. Oocytes are then retrieved and can be cryopreserved or fertilised in vitro with a pre-prepared sample of the partner's semen or a sperm donor. The resulting embryos are then classified according to morphological and cellular kinetics parameters of development/division; the better the embryo's class, the higher the implantation chances [54]. These embryos can be transferred in the same cycle or cryopreserved, and the remaining good quality embryos can also be cryopreserved for further cycles, if necessary. Indeed, the recent evolution and optimisation of cryopreservation processes have enabled equivalent results in terms of cumulative LBR with frozen-thawed embryos and fresh embryo transfers [55]. Importantly, cumulative LBR is a suitable concept for reporting the success of an IVF programme incorporating fresh and thawed embryo transfers. In contrast with the conventionally reported chance of pregnancy and delivery per cycle or per embryo transfer, the cumulative LBR captures the totality of live births after successive treatment. Since this term better summarises the chance of a live birth over the entire assisted reproduction process, it is most appropriate from the couple's perspective [56]. Moreover, cumulative LBR supports reducing the number of embryos per transfer [57]. This should be explained and considered in people with MS to avoid multiple pregnancy risks and dampen the psychological impact of potential unsuccessful implantation.

In relation to men with MS, the ART technique (IVF or IUI) decided upon will also depend on the couple's characteristics, but the management is more straightforward in men than in women. In general, DMT do not affect male fertility and are usually not withdrawn when the patient expresses a desire for fatherhood [58]. Nevertheless, in the case that a proven effect of the DMT on sperm quality is observed, the therapy could be switched, and after waiting for a potential washout period, the patient's sperm sample could be frozen before the original DMT is reinitiated. In addition, sexual dysfunction is common in men with MS

and can stem directly from the demyelinating lesions caused by MS (e.g. erectile and ejaculatory dysfunction, numbness, sensory paresthesias) or be secondary to the disease (e.g. fatigue, spasticity, bowel dysfunction) [59]. Regardless, a sperm sample can be collected for the purpose of IVF by electroejaculation, in cases of physical impairments, or testicular biopsy, if the patient presents ejaculatory issues (Table 1) [60].

Oocyte Cryopreservation

As mentioned above, oocytes retrieved after ovulation induction can be cryopreserved for future use. OC is a relatively new ART from which women with MS can benefit. In women requiring ART and presenting a pre-existing disease that can force them to delay their desire for motherhood, OC can be considered a reasonable option. Thus, trends of OC in oncologic patients have increased over recent years [61], as have, most likely, those in women with endometriosis, although data are scarce for this patient population [62]. However, early pregnancy (stemming from an early, well-planned preconception counselling) is much more cost-effective than OC, even in women with pre-existing pathologies.

The OC process is similar to the IVF process and uses the same drugs described above for ovarian stimulation. Similar to IVF, after performing the appropriate controls, oocyte extraction is undertaken in an operating room. However, contrary to IVF, the next step is ultrafast freezing (vitrification) of non-fertilised oocytes, which can remain vitrified indefinitely. Alternatively, oocytes can be fertilised before vitrification, resulting in indefinite preservation of the resulting embryos, although embryo cryopreservation could clash with personal religious or moral beliefs [63].

Notwithstanding the above points and according to data based on social cryopreservation (i.e. OC in women without any pathology), as well as considering the experience in the field with women with endometriosis, OC can be beneficial to women with MS as long as they meet certain criteria [64]. First and foremost, the age at which they undertake OC is crucial:

the older the woman, the higher the number of vitrified oocytes required to increase the LBR [65]. Therefore, OC is recommended in women younger than 35–37 years old, with data showing that women aged 37 years maximum reap the highest benefit over electing not to cryopreserve oocytes [66]. From that age onwards, the delay of motherhood in terms of ovarian quality and decline in fertility is more marked [66, 67]. Second, OC can benefit women with a decent number of oocytes that can be retrieved with a reasonable number of stimulations; as for IVF, three oocytes are generally considered to be the maximum to be retrieved. Therefore, women must, ideally, present moderate-good ovarian reserve, estimated by their levels of anti-Müllerian hormone and antral follicle count assessed by transvaginal ultrasound [66, 67]. Women fulfilling these requirements also have a higher probability of needing their frozen oocytes than those who do not fulfil them. In addition, women with MS who are compelled to delay motherhood for ≥ 1 years (e.g. because their MS is not under control, they have been on DMT for a short time or their DMT has a long wash-out period) are also eligible for OC. Therefore, women with MS could benefit from “fertility preservation” programmes (spontaneous fertility cannot be restored nor preserved) based on medical reasons (Table 1).

Multidisciplinary Units

For people with MS, time without DMT can be crucial. Thus, anticipation of motherhood through early family planning is vital in order that the patient remain without her DMT for the shortest possible time. From the ART perspective, the management of some people with MS can be complex because they may suffer relapses if DMT are withdrawn. Consequently, if women needing ART have a pre-existing pathology, as in people with MS, a multidisciplinary approach is justified. In addition, excellent neurology-gynaecology bidirectional communication is essential to coordinate DMT timing and ART in these patients.

Multidisciplinary units have been put forward as the best management option for a

disease as complex as MS [68]. In people with MS diagnosed in their reproductive years, which represent the lion’s share of MS patients, these multidisciplinary units are vital to addressing their needs. The specialists involved in these multidisciplinary units should be diverse and include specialists in addition to neurologists and gynaecologists. For example, social care workers may be needed in some instances to help evaluate the suitability of the couple to care for a child. Indeed, the ethical implications of pregnancy in people with MS are numerous [69, 70]. Although pregnancy should be generally supported and managed by physicians [71], the latter should ponder their duty to the patient, the foetus and the healthcare system to provide the best counselling [72]. Ultimately, pregnancy in women with MS should be assessed on a case-by-case basis. Importantly, it is in the best interest of people with MS that multidisciplinary care units are formed with good coordination and communication among all specialists involved in managing their disease (Table 1). If such units are unavailable, we consider that people with MS and parenthood desire should still be managed, as much as possible, by all of the abovementioned specialists, although the coordination and communication between these specialists might be deficient in these cases.

Limitations

Given that data analysing ART in people with MS are limited, the main limitation of our recommendations is that they are chiefly based on experts’ reproductive-assisted experience in women without MS. However, in a recent large populational study, the chance of a live birth with ART in women with MS was found to be similar to that of women without MS [73]. Nonetheless, further research is needed to analyse, in large observational and prospective studies, the impact and efficacy of ART regarding some important aspects of MS (e.g. relapses, disability scores, potential effects and interactions of corticosteroids and other DMT during ART). Finally, our recommendations were provided by Spanish neurologists and

gynaecologists and, albeit our belief they can be extended to other Western European countries, the specific characteristics of people in regions other than Spain may preclude their generalisability.

CONCLUSIONS

Multiple sclerosis is mainly diagnosed in women of childbearing age, but the disease does not directly affect the pregnancy course and, therefore, does not necessarily deter pregnancy. However, because women with MS must wait for a period of low clinical and radiological activity, they tend to delay their desire for motherhood. Since age strongly impacts a woman's fertility, an early preconception consultation is paramount to provide people with MS and their partners with tools to achieve a shared decision on a future pregnancy. Regarding treatment, if clinically indicated, interferon beta and glatiramer acetate can be considered throughout pregnancy, and natalizumab can be used up to the third trimester, provided that their benefits to the patient outweigh their risks to the foetus. In addition, antiCD20, albeit supported by limited data, can also be envisaged as therapy on a case-by-case basis. Because women with MS are often older than the general population when ready to become mothers, they are more likely to require ART. In this context, IVF-ICSI is the most widely used technique in people with MS and is considered safe for both men and women. Also, GnRH antagonist protocols are currently preferred in ovarian stimulation procedures to avoid unnecessary risks. OC or embryo cryopreservation are alternatives procedure to ponder in the cases of young women recently diagnosed with MS who will have to delay their desire for motherhood. Bearing in mind that an early, well-planned, spontaneous pregnancy should always prevail as the best option, the best candidates for OC are women aged around 35–37 years, with a moderate-good ovarian reserve, who are willing and able to delay their pregnancy 12–18 months. In addition, good neurology–gynaecology coordination is crucial to avoid the risk of relapse that could result from an

extended period off treatment. Finally, the management of women with MS with the desire for motherhood by multidisciplinary units is warranted to guide them appropriately through the course of their pregnancy.

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