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Expert opinion on the use of contraception in people with multiple sclerosis

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Abstract

Background: Current guidance on the selection of appropriate contraception for people with multiple sclerosis (PwMS) is lacking.

Objective: To address this gap, an expert-led consensus program developed recommendations to support clinicians in discussing family planning and contraception with women and men with multiple sclerosis (MS).

Methods: A multidisciplinary steering committee (SC) of 13 international clinical experts led the program, supported by an extended faculty of 32 experts representing 18 countries. A modified Delphi methodology was used for decision-making and consensus-building. The SC drafted 15 clinical questions focused on patient-centered care, selection of contraception, and timing of stopping/starting contraception and disease-modifying therapies (DMTs). Statements addressing each question were drafted based on evaluation of published evidence and the experts' clinical experience. Consensus was reached if $\geq 75\%$ of respondents agreed (scoring 7–9 on a 9-point scale) with each recommendation.

Results: Consensus was reached on 24 of 25 proposed recommendations, including how and when to discuss contraception, types and safety of contraceptives, and how to evaluate the most appropriate contraceptive options for specific patient groups, including those with significant disability or being treated with DMTs.

Conclusion: These expert recommendations provide the first practical, relevant, and comprehensive guidance for clinicians on the selection of contraception in PwMS.

Keywords: Multiple sclerosis, contraception, disease-modifying therapy, consensus, expert opinion, reproductive health

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Introduction

Multiple sclerosis (MS) typically occurs during child-bearing years.^{1,2} Women and men with MS have a unique set of factors to consider during family planning and when choosing contraception.^{1–3}

People with multiple sclerosis (PwMS) may want to delay or prevent pregnancy for several reasons.^{3,4} Conception is not advised during treatment with potentially gonadotoxic or teratogenic disease-modifying therapies (DMTs) because of potential risks to the embryo/fetus.^{5–7} However, stopping certain DMTs (e.g. natalizumab, fingolimod) without providing an alternative effective treatment can increase the risk of rebound relapse.⁸ Furthermore, pregnancy can affect

the course of MS, lowering the risk of relapse between the first and third trimester but increasing the risk of relapse postpartum in some patients.^{3,4} Counseling with a multidisciplinary team (MDT) can help PwMS evaluate their options for safe and effective contraception and other family planning decisions, including optimal timing of discontinuation/resumption of MS therapies.^{2,5,9,10}

Current contraceptive guidelines do not include specific recommendations for PwMS and provide limited guidance on the options and practicalities that are most appropriate for this patient group.^{11–15} Consensus-based recommendations can guide clinicians where there are gaps in published guidelines.

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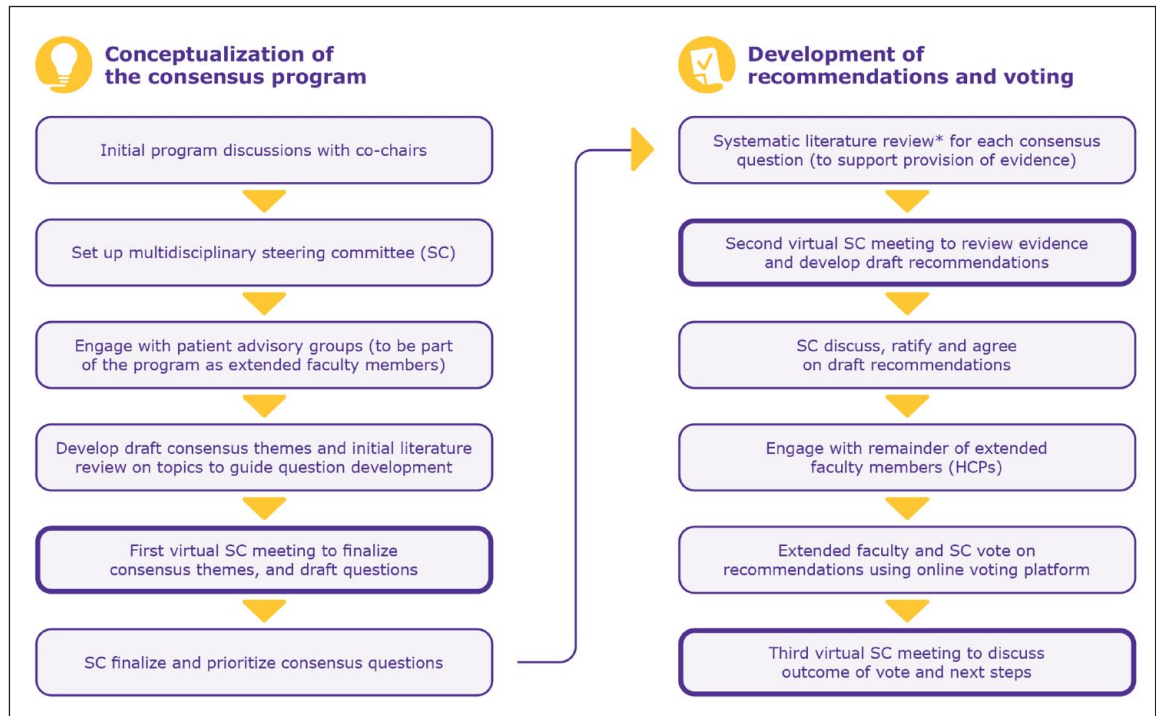


Figure 1. Overview of the modified Delphi process for achieving consensus (modified from Sørensen et al.¹⁶).

HCP: healthcare professional; PICO: population, interest, context; PICO: population, intervention, comparison, outcome; SC: steering committee.

*A PICO/PICo framework was used for each question, to inform the systematic literature review.

Here, we describe a consensus-based program, led by a group of international experts, designed to provide practical recommendations relating to contraception for women and men with MS. The recommendations focus on three topics: patient-centered care, selection of contraception for PwMS, and timing of stopping/starting contraception and DMTs.

A plain language summary video of the program and results can be found in the supplementary materials.

Materials and methods

The consensus program was based on a modified Delphi methodology as described by Sørensen et al.¹⁶ (Figure 1). A multidisciplinary steering committee (SC) of 13 international clinical experts led the program, co-chaired by Jan Hillert and Manuela Simoni. Three meetings took place between November 2021 and April 2022.

After an initial review of published literature on contraception and MS, the SC convened to discuss and agree on the consensus themes, and developed 15 clinical questions. An in-depth systematic literature review (SLR; Supplementary methodology) was

performed to address the 15 questions, using the PICOS (population, interventions and comparisons, outcomes of interest, and study design) framework (Supplementary Table S1). Evidence levels were assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) rating scale.¹⁷ The level of evidence for each question was dependent on the number of references identified in the SLR: low (0–9), medium (10–19), and high (≥ 20).

After reviewing the evidence, the SC drafted clinical recommendations for each question. An extended faculty (EF) of 91 clinical experts were invited to vote on the clinical recommendations, with the aim of an EF participation rate of ~25%. EF members were selected based on their publications and research interests, and recommendations from the SC. Of the EF, 32 experts from 18 countries participated, and included nurses, patient advisory groups, neurologists, and gynecologists (participation rate, 35.2%).

SC ($n = 12$) and EF ($n = 32$) members voted on clinical recommendations ($N = 44$) using an online platform. Consensus was achieved when $\geq 75\%$ of respondents agreed in the range of 7–9 (9-point scale). Each

statement/recommendation received a strength score (median) and consensus level (% of votes with a score of 7–9).¹⁸ Responders were asked to provide their rationale for scores of ≤ 6 ; those who felt unqualified to vote could select “not applicable.”

Results

The process of identifying and selecting literature is summarized in Supplementary methodology and Supplementary Figure S1. First-pass screening (title and/or abstract based) of 142 citations identified 75 relevant articles. Most articles (84%) were published between 2011 and 2022. Of the 72 full-text publications and 3 congress abstracts, there were 33 original articles (Supplementary results), 34 reviews, 3 SLRs, 4 recommendations, and 1 commentary.

The SC drafted 25 recommendations for voting on three themes: patient-centered care, selection of contraception for PwMS, and timing of stopping/starting contraception and DMTs. After one round of voting, consensus was reached on 24/25 recommendations, with 11 reaching 90%–100%, 12 achieving 80%–89%, and 1 in the range of 75%–79%. All but one SC member voted on all questions. Twenty-three (52.3%) respondents deemed themselves “not qualified” to vote on ≥ 1 recommendation and selected “not applicable.” Therefore, the number of experts voting on each recommendation ranged from 27 to 44 participants.

Key evidence for each question is summarized below, and the clinical recommendations are provided in Tables 1–3. Supplementary Tables S2–S4 list respondent reasons for scores ≤ 6 . Supplementary Table S5 summarizes SLR outputs for each question.

Patient-centered care

Question 1: what is the population of PwMS with whom contraception issues should be discussed, and when should discussion take place? The effects of MS on fertility have not been fully determined. The general consensus is that fertility is not significantly affected in PwMS.^{6,7,19} For this reason, contraception in PwMS is important for those who want to avoid pregnancy and/or to avoid any DMT risk on a potential pregnancy.^{5,19} Family planning is an important step for women and men with MS and counseling on contraception should be offered at diagnosis and regularly throughout a patient’s follow-up.^{1,5,9,19}

Question 2: who should be included in the discussion and decision-making process with PwMS about contraception? Discussing contraception for PwMS may

involve an MDT of neurologists, obstetricians/gynecologists, and nurses. However, in some practices, certain MDT members may be more relevant and necessary for the conversation than others.^{1,2,4,9,19} Although neurologists are not expected to prescribe contraceptives, they may help patients make reasonable contraceptive choices while considering MS-specific factors, such as level of disability and co-administered medications.¹

Question 3: what topics should be included in the contraception discussion for PwMS? A wide range of topics should be discussed, including the benefit–risk profile of DMTs before, during, and after pregnancy, the patient’s desired timing of pregnancy in relation to disease course and activity, and the full range and effectiveness of contraceptive methods suitable for their individual profile.^{1,19}

Some important topics listed within the recommendations for Question 3 are not specific to PwMS. Not all PwMS will be affected by issues, including teratogenic DMTs and sexually transmitted infections (STIs), but it is important to provide the opportunity to discuss if needed.

Selection of contraception for PwMS

Question 4: what factors should be taken into account when deciding the choice of contraception in PwMS? It is important to consider safety, availability, acceptability, and effectiveness, as well as relevant disabilities, such as dysphagia, when choosing contraception.^{1,15,19} The role of male and female condoms in preventing STIs should also be considered.¹⁵

Question 5: what is the key consideration for prescribing a DMT that will be used in women of child-bearing potential (WOCBP) with MS? Most DMTs are not known to interact with or decrease the effectiveness of hormonal contraception.^{1,6,20} Some DMTs, for example, cladribine tablets, teriflunomide, and sphingosine-1-phosphate receptor modulators (such as fingolimod) have known risks in pregnancy, while for others (natalizumab, ocrelizumab, dimethyl fumarate, alemtuzumab) there is not enough evidence about their safety in pregnancy and contraception should still be advised.^{5,6,21,22} If interferon β and/or glatiramer acetate are prescribed to WOCBP, contraception is not necessary as these drugs can be used until conception.⁶ Table 4 summarizes recommendations for reproductive health for PwMS based on known gonadotoxicity/teratogenicity of DMTs detailed in Massarotti *et al.*⁷ and Dobson *et al.*⁶

Table 1. Clinical recommendations to address clinical questions on patient-centered care.

Question Clinical recommendation	Strength of recommendation ^a Median score (mean)	Level of consensus ^b Percentage of respondents in agreement (number of respondents)
<p>Question 1: What is the population of PwMS with whom contraception issues should be discussed, and when should discussion take place? (Level of evidence: Medium)^c</p> <p>CR1: Family planning for PwMS should be discussed at the time of diagnosis and on a regular basis to ensure informed decisions are made. This should include the use of contraception for PwMS who wish to and/or need to avoid pregnancy, particularly if a teratogenic or gonadotoxic treatment is used. PwMS should be invited to include their partners in such discussions, when appropriate.</p>	9 (8.8)	97.7% N=43/44
<p>Question 2: Who should be included in the discussion and decision-making process with PwMS about contraception? (Level of evidence: Medium)^c</p> <p>CR2: All discussions and decisions regarding family planning and contraception should be comprehensive and tailored to the individual PwMS. It is advantageous to include several members of the multidisciplinary team at key stages, including obstetricians/gynecologists, neurologists, general practitioners, clinical nurse specialists, pharmacists, and social workers, as appropriate.</p>	8 (7.9)	86.4% N=38/44
<p>Question 3: What topics should be included in the contraception discussion for PwMS? (Level of evidence: High)^c</p> <p>CR3: Topics in the contraception discussion that are specific to PwMS must include the importance of effective contraception when using a DMT or other treatment that is stated as being potentially teratogenic or gonadotoxic in the label, and/or has other safety concerns. A desired pregnancy should be planned and a potential switch/stop of MS medication needs to be performed in time in line with label recommendations.</p> <p>CR4: In addition, more general topics around contraception may also be considered, as appropriate to the individual patient, including:</p> <ul style="list-style-type: none"> • The potential consequences of an unplanned pregnancy and protection against sexually transmitted infections. <p>CR5:</p> <ul style="list-style-type: none"> • The effectiveness and risk–benefit balance of the available range of contraceptive options. 	9 (8.3)	88.6% N=39/44
	9 (8.1)	88.6% N=39/44
	8 (7.8)	83.3% N=35/42
<p>PwMS: people with multiple sclerosis; CR: clinical recommendation; DMT: disease-modifying therapy; MS: multiple sclerosis; SLR: systematic literature review. ^aMedian score on a 1–9 scale. ^bPercentage of votes with 7–9 on a 9-point scale. ^c“Level of evidence” defined based on the following grading of references identified by SLR review: high when supported by ≥20 references; medium when supported by 10–19 references; and low when supported by 0–9 references.</p>		

Question 6: what considerations should be given when discussing long-acting reversible contraception (LARC) as an option for WOCBP with MS? In women receiving potentially teratogenic DMTs,

LARC may be recommended to prevent drug-exposed pregnancies due to its long-lasting high efficacy, reliability, and convenience.^{1,3,9,23} LARC may be particularly suitable for PwMS who cannot be

Table 2. Clinical recommendations to address clinical questions on selection on contraception for PwMS.

Question Clinical recommendation	Strength of recommendation ^a Median score (mean)	Level of consensus ^b Percentage of respondents in agreement (number of respondents)
Question 4: What factors should be taken into account when deciding the choice of contraception in PwMS? (Level of evidence: High) ^c		
CR6: When deciding on the method of contraception, several factors should be considered including: • Contraceptive factors; the efficacy of the contraceptive, potential interactions with DMTs and other medications; the effect of the method of contraception on libido, mood and bleeding patterns, and potential risks such as cardiovascular events.	9 (8.2)	95.3% N=41/44
CR7: • Patient's clinical characteristics including age, sex, body mass index, immobility, risk of relapse, bone health, disease stage, family history of cardiovascular disease, gynecological history, and ability to swallow tablets.	9 (8.3)	94.9% N=37/39
CR8: • Patient preferences and social factors; patient's family plans, preferred method(s) of contraception, and available insurance coverage where relevant.	8 (8.4)	95.0% N=38/40
Question 5: What is the key consideration for prescribing a DMT that will be used in WOCBP with MS? (Level of evidence: High) ^c		
CR9: When prescribing a DMT that will be used in WOCBP with MS, the key considerations are the potential for relapse and whether the label for the DMT states that there is potential for fetal harm and an associated need for effective contraception. It is also important to consider any potential interactions between the DMT and the contraception.	9 (8.4)	88.6% N=39/44
Question 6: What considerations should be given when discussing LARC as an option for contraception with WOCBP with MS? (Level of evidence: Low) ^c		
CR10: LARC, including IUDs and implants, are an effective method of contraception and may be included as an option during family planning discussions. LARC may have particular utility for WOCBP with MS with mobility issues due to the reduced risk of thrombosis compared with other methods of contraception, as well as those WOCBP with MS who are currently receiving DMTs with teratogenic potential.	9 (8.3)	92.3% N=36/39
Question 7: What are the considerations when discussing CHC as an option with WOCBP with MS? (Level of evidence: Low) ^c		
CR11: CHCs (i.e. contraceptives combining estrogen and progestin) can be associated with blood clots and are therefore not recommended for WOCBP with MS with significant risk of VTE or prolonged immobility.	8 (8.1)	90.0% N=36/40
Question 8: Can CHC or progestin-only contraception be prescribed to women with MS to help regulate their MS symptoms? (Level of evidence: Low) ^c		
CR12: Limited evidence suggests that exogenous hormones including oral contraception (e.g. combined contraceptive pill and the progestin-only pill), may potentially help stabilize MS symptoms that fluctuate during the menstrual cycle. The combined contraceptive pill can be either continuous (3 months before a pill-free or placebo break) or cyclic (1 month followed by a pill-free or placebo break). The progestin-only pill is taken continuously. More research is required in this area.	7 (7.2)	82.1% N=32/39

(Continued)

Table 2. (Continued)

Question Clinical recommendation	Strength of recommendation ^a Median score (mean)	Level of consensus ^b Percentage of respondents in agreement (number of respondents)
Question 9: What are the considerations when discussing progestin-only contraception as an option with WOCBP with MS? (Level of evidence: Low) ^c		
CR13: The following should be addressed when considering initiation of progestin-only contraception in WOCBP with MS: • the specific type of progestin	7 (7.1)	74.1% N=20/27
CR14: • fluctuation of MS symptoms	7 (7.1)	82.1% N=23/28
CR15: • the role of breakthrough bleeding	8 (7.6)	82.1% N=23/28
CR16: While some studies have reported the changes in bone mineral density with DMPA to be reversible with discontinuation, given the higher risk of reduced bone mineral density among PwMS, consideration of additive impact for those with osteopenia or osteoporosis should be considered.	8 (8.0)	88.9% N=32/36
Question 10: What considerations should be given when discussing contraception options for male PwMS? (Level of evidence: Low) ^c		
CR17: Certain DMTs (cladribine tablets; teriflunomide) have been associated with male-mediated fetal toxicity in preclinical studies. The US and EU labels make varying recommendations. The applicable label should be closely consulted before advising male PwMS prescribed these DMTs on any methods of contraception. For heterosexual relationships, if contraception is advised, due to the risk of transfer it should be made clear that a barrier method should be used regardless of the female partner's use of contraceptives.	8.5 (7.8)	84.1% N=37/44
Question 11: What methods, if any, of contraception should be recommended against in PwMS? (Level of evidence: Low) ^c		
CR18: Methods of contraception which should not be recommended will be dependent on the PwMS and their risk profile. Overall, WOCBP with MS who have mobility issues should avoid using CHC, and PwMS with decreased bone mineral density should avoid DMPA injections.	8 (7.9)	87.5% N=35/40
CR19: In addition, less effective methods such as fertility awareness and withdrawal should be considered carefully in PwMS receiving a DMT or any other treatment that is stated as being potentially teratogenic or gonadotoxic in the label or is associated with other patient-specific safety concerns.	9 (7.5)	78.6% N=33/42
Question 12: What are the key overall considerations for methods of contraception in WOCBP with MS who have high levels of disability? (Level of evidence: Medium) ^c		
CR20: When prescribing contraception, it is important to consider that WOCBP with MS who have high levels of disability are more likely to be older, peri-or post-menopausal, at increased risk of obesity, and may have reduced bone mineral density. In the perimenopausal stage, fertility is lower with irregular menstrual cycles and therefore condoms or the progestin-only pill may be considered, as well as LARC (IUDs and implants), depending on fertility desires. Women with MS and their partners may want to consider sterilization if they do not wish to have children in the future.	8 (7.8)	95.2% N=40/42

(Continued)

Table 2. (Continued)

Question Clinical recommendation	Strength of recommendation ^a Median score (mean)	Level of consensus ^b Percentage of respondents in agreement (number of respondents)
CR21: CHC should be avoided in female PwMS with immobility due to VTE risk.	8 (8.0)	95.1% N=39/41
CR22: DMPA should be avoided in older PwMS with immobility and/or low bone density.	8 (7.8)	89.7% N=35/39
Question 13: What factors should be considered before prescribing a method of emergency contraception to WOCBP with MS? (Level of evidence: Low) ^c		
CR23: Emergency contraception can be used in WOCBP with MS and needs to be taken or placed as soon as possible after unprotected intercourse to be effective. Options are the emergency contraceptive pills (levonorgestrel or ulipristal acetate) as well as the IUD (levonorgestrel or copper containing).	8 (8.0)	91.9% N=34/37

CR: clinical recommendation; DMT: disease-modifying therapy; WOCBP: women of childbearing potential; MS: multiple sclerosis; LARC: long-acting reversible contraception; IUD: intrauterine device; CHC: combined hormonal contraception; VTE: venous thromboembolism; DMPA: depot-medroxyprogesterone acetate; SLR: systematic literature review; PwMS: people with multiple sclerosis.

^aMedian score on a 1–9 scale.
^bPercentage of votes with 7–9 on a 9-point scale.
^c“Level of evidence” defined based on the following grading of references identified by SLR review: high when supported by ≥20 references; medium when supported by 10–19 references; and low when supported by 0–9 references.

Table 3. Clinical recommendations to address clinical questions on the timing of stopping/starting contraception and disease-modifying therapies.

Question Clinical recommendation	Strength of recommendation ^a Median score (mean)	Level of consensus ^b Percentage of respondents in agreement (number of respondents)
Question 14: When should contraception be considered in relation to starting DMTs in PwMS? (Level of evidence: Low) ^c		
CR24: Before starting or changing to a DMT that is stated as being potentially teratogenic or gonadotoxic in the label or has other safety concerns, the appropriate methods of contraception should be discussed with the PwMS in line with the DMT label. This is important as MS does not significantly affect the ability to conceive.	9 (8.6)	97.7% N=43/44
Question 15: What is the optimum washout period after discontinuation of DMT and hormonal contraception prior to conception in PwMS? (Level of evidence: Medium) ^c		
CR25: The optimum washout period after discontinuation of a DMT before attempting to conceive is dependent on the type of DMT. Label recommendations should be followed. Contraceptive options should be discussed and combined with individual decision-making. Effective contraception should be used until the recommended DMT washout period is complete.	9 (8.3)	90.7% N=39/43

DMT: disease-modifying therapy; PwMS: people with multiple sclerosis; CR: clinical recommendation; MS: multiple sclerosis; SLR: systematic literature review.

^aMedian score on a 1–9 scale.
^bPercentage of votes with 7–9 on a 9-point scale.
^c“Level of evidence” defined based on the following grading of references identified by SLR review: high when supported by ≥20 references; medium when supported by 10–19 references; and low when supported by 0–9 references.

prescribed combined hormonal contraception (CHC) (see Question 7).

Question 7: what are the considerations when discussing CHC as an option for WOCBP with MS? The use of CHC has not been shown to worsen MS disease course.¹ However, users of CHC may have increased risk of venous thromboembolism (VTE)—these risks are enhanced with immobility, and therefore, CHC should be avoided in MS patients with reduced mobility and/or those at risk of VTE.⁹ Furthermore, if PwMS are immobile but do not have a history of blood clots, CHC is still not advisable.

Question 8: can CHC or progestin-only contraception be prescribed to women with MS to help regulate their MS symptoms? There are limited data in the literature surrounding this topic. Some studies suggest an improvement in MS symptoms with CHC or progestin-only contraception, although these studies were observational, so bias may have influenced the results.^{24–26} Others have proposed that premenstrual hormonal changes may worsen symptoms in people with relapsing-remitting MS.²⁷

Question 9: what are the considerations when discussing progestin-only contraception as an option for WOCBP with MS? Breakthrough bleeding, or unscheduled bleeding, is an important factor to consider with progestin-only contraceptives and PwMS should be made aware of this.²⁸ As depot-medroxyprogesterone acetate (DMPA) may compromise bone health,^{1,19} its use should be carefully considered in patients who are at risk of osteopenia (patients with a family history of, or who are older in age), despite reports that the effects of DMPA on bone mineral density are reversible.²⁹ Women with MS and a history of repeated and excessive use of corticosteroids, and immobility may also be at risk of osteopenia and osteoporosis; bone mineral density in these individuals should be assessed before initiation of DMPA.

Question 10: what considerations should be given when discussing contraception options for male PwMS? The effects of MS and DMTs on fertility are not fully understood and are particularly under-investigated in men.⁷ There is, however, clear contraceptive guidance for men using cladribine tablets and/or teriflunomide. Men taking cladribine tablets must use effective contraception with female partners to avoid pregnancy during treatment and up to 6 months after the last dose.⁹ Men who wish to conceive with their female partners should discontinue teriflunomide.⁹

Question 11: what methods, if any, of contraception should be recommended against in PwMS? In PwMS receiving potentially teratogenic or gonadotoxic DMTs, an effective method of contraception is recommended.^{6,9,10} Oral contraceptives do not increase the risk of MS or increase the risk of relapse.³ CHC is not recommended for women with MS with prolonged immobility, due to an increased risk of VTE, or who have difficulty swallowing.¹⁰ DMPA is associated with decreased bone mineral density and not recommended in women with osteopenia or osteoporosis.¹ Female patients with impaired fine motor function may experience difficulty with vaginal rings and diaphragms, so another method of contraception may be preferred.¹

Question 12: what are the key overall considerations for methods of contraception in WOCBP with MS who have high levels of disability? For women with MS with prolonged immobility, CHC is not usually recommended due to VTE risk, and DMPA may further compromise bone mineral density.¹ Tolerability and bleeding patterns are also important to consider with all methods of contraception.

Question 13: what factors should be considered before prescribing a method of emergency contraception to WOCBP with MS? There is a lack of evidence on this topic for PwMS. In general, emergency oral contraception options are typically levonorgestrel or ulipristal acetate. The copper intrauterine device (IUD) appears to be more effective than oral methods as an emergency contraceptive.³⁰ A study has shown that the levonorgestrel IUD was noninferior to the copper IUD for emergency contraception.³¹

Timing of stopping/starting contraception and DMTs

Question 14: when should contraception be considered in relation to starting DMTs in PwMS? Each DMT label outlines the precautions to be taken when starting therapy.⁶ In most cases, contraception is recommended when starting a DMT due to limited safety information.^{6,20,32} The efficacy of hormonal contraceptives is not affected by the use of DMTs.^{2,3,6}

Question 15: what is the optimum washout period after discontinuation of DMT and hormonal contraception prior to conception in PwMS? Each DMT label has recommendations on washout before conception.^{1,2,5,6} DMTs with potential teratogenicity or those contraindicated in pregnancy should be discontinued and replaced with acceptable alternative treatment before conception.^{2,19,20} If the decision is made

Table 4. Summary of commonly used disease-modifying therapies and their gonadotoxicity and teratogenicity, based on Dobson *et al.*⁶ and Massarotti *et al.*⁷ (please refer to the most recent label for current prescribing information).

DMT	Contraception advised? (Yes/No)	Contraception advised in men? (Yes/No)	Interactions with hormonal contraception? (Yes/No)	Reproductive health recommendations related to gonadotoxicity/teratogenicity
IFN β and GA (Avonex, Betaferon, Extavia, Plegridy, Rebif, Copaxone)	No	No ^a	No	<ul style="list-style-type: none"> Treatments can be continued at least up until conception. There is no evidence for the need of termination if unplanned pregnancy occurs while taking IFN β/GA.
Natalizumab (Tysabri)	No ^b	No ^{b,c}	No	<ul style="list-style-type: none"> No specific pattern of birth defects have been observed in patients receiving natalizumab during pregnancy to suggest it is teratogenic.
Fingolimod (Gilenya)	Yes	Not enough data for a clinical recommendation	No	<ul style="list-style-type: none"> Limited information about the safety of fingolimod in pregnancy is available. Women with MS planning to become pregnant should be advised to stop fingolimod at least 2 months before conception. Alternative treatments to minimize the risk of discontinuation rebound should be discussed.
Teriflunomide (Aubagio)	Yes	Yes ^d	No	<ul style="list-style-type: none"> Women wishing to conceive who have received teriflunomide should discontinue it and undergo an accelerated elimination procedure, as teriflunomide has a very long enterohepatic circulation. Women with MS should remain on contraception for at least 6 weeks after serum drug concentrations have been shown to be <0.02 mg/L on two occasions at least 14 days apart. Teriflunomide is teratogenic in animals at equivalent doses to those given to humans. Therefore, caution should be advised when prescribing this to women of childbearing age. Women with MS should be advised that they must use effective contraception while receiving teriflunomide and for 2 years after discontinuation, unless they have undergone an accelerated elimination procedure. Men with MS should be advised that teriflunomide can reduce sperm counts. Furthermore, male-to-female transfer of sperm may lead to low levels of teriflunomide being present in the female.
Dimethyl fumarate (Tecfidera)	Yes	Not stated	No ^e	<ul style="list-style-type: none"> There are limited data about the safety of dimethyl fumarate in pregnancy. Women with MS should use effective contraception while receiving this therapy and if they do become pregnant, they should only continue treatment if the potential benefit justifies the potential risk to the fetus. Women with MS wishing to become pregnant should be advised to consider switching to an alternative treatment.
Ocrelizumab (Ocrevus)	Yes	Not stated	No	<ul style="list-style-type: none"> In the EU, it is recommended that women should use contraception while receiving ocrelizumab and for 12 months after the last infusion. As ocrelizumab is a humanized monoclonal IgG antibody and can cross the placenta, fetal exposure is likely during later stages of pregnancy, once placenta is formed.

(Continued)

Table 4. (Continued)

DMT	Contraception advised? (Yes/No)	Contraception advised in men? (Yes/No)	Interactions with hormonal contraception? (Yes/No)	Reproductive health recommendations related to gonadotoxicity/teratogenicity
Alemtuzumab (Lemtrada)	Yes	Not stated	No	<ul style="list-style-type: none"> Manufacturers recommend that women with MS should use effective contraception for 4 months following a course of treatment with alemtuzumab. If pregnancy occurs within a month of treatment, increased obstetric monitoring is advised. Women with MS should not be treated with alemtuzumab during pregnancy or while breastfeeding.
Cladribine (Mavenclad)	Yes	Yes	No	<ul style="list-style-type: none"> Manufacturers recommend that women using hormonal contraception should add a barrier method of contraception during cladribine treatment and for at least 4 weeks after the last dose in each treatment year. Women should be advised not to become pregnant for at least 6 months following a course of cladribine. Due to cladribine's effect on DNA synthesis, male partners must take precautions to prevent pregnancy of their partner during cladribine treatment and for at least 6 months after the last dose.

DMT: disease-modifying therapy; IFN β : interferon beta; GA: glatiramer acetate; MS: multiple sclerosis; IgG: immunoglobulin G.

^aMen can continue using IFN β -1a, IFN β -1b, and GA without contraception if the benefits outweigh the risk. No washout period is required.

^bThere is no evidence in human studies that natalizumab results in reduced fertility or congenital malformations.

^cMen can continue to use natalizumab without contraception if the benefits outweigh the risk. No washout period is required.

^dTeriflunomide has been shown to be teratogenic and can be transferred sexually. This drug should be avoided in men trying to conceive.

^eDimethyl fumarate may reduce efficacy due to gastrointestinal side effects which can occur within the first few weeks of treatment. Additional contraceptive measures are advisable in case of interference with absorption of the contraceptive pill/oral contraceptives (both combined estrogen and progestin, and progestin-only pill).

to stop DMT or to switch to an alternative treatment before conception, PwMS will usually be required to complete a washout period; contraception should be continued until the washout is complete.³³ Patients may be advised for their DMT washout periods to be as short as possible to prevent relapses.^{10,23}

However, healthcare professionals (HCPs) should be cautious and not underestimate the time required for washout. Once the DMT washout is completed, contraception can be stopped to minimize the period without treatment before conception.³³ Consequently, preconception care, such as folic acid supplementation, may be needed before stopping contraception.^{34,35}

Discussion

The clinical recommendations described by this consensus provide practical advice on contraception to support HCPs involved in the care of PwMS. The current data and therefore recommendations made apply to cisgender women and men with MS. Additional data are needed on gender-diverse patient populations, including transgender and non-binary populations. In

this consensus, the faculty of 44 clinical experts from 19 countries voted on the 25 recommendations, giving quality and strength to their relevance. All but one of the recommendations achieved consensus ($\geq 75\%$).

The one recommendation that did not achieve consensus (74.1%) was around the considerations when discussing progestin-only contraception as an option for WOCBP with MS (clinical recommendation [CR] 13, Table 2). The faculty commented that the specific type of progestin is rarely considered by HCPs, the relevance of different types of progestins is unknown, and effectiveness and cost are usually of greatest importance (Supplementary Table S3). It is important to note that consensus was missed by a small margin (0.9%).

The strongest clinical recommendations supported by the highest levels of evidence (and 83%–95% expert consensus) were recommendations on which factors to consider when making contraception decisions, including contraceptive efficacy, impact on mood, libido and physical health, potential risks, and patient clinical characteristics and preferences (CR6, 7, and 8), and on the key considerations for DMT

prescription for WOCBP (CR9). There is also strong evidence to support the recommendation for contraceptive conversations with PwMS, which emphasize the need for discussion on effective contraception during DMT use and address safety concerns, including consequences of unplanned pregnancy and protection against STIs, while evaluating effectiveness and risk–benefit of each contraceptive method (CR3, 4, and 5). However, a number of recommendations are based predominantly on expert opinion and clinical practice. Therefore, further clinical research is advocated to investigate:

- The benefits of LARC for patients with mobility issues and WOCBP on potentially teratogenic DMTs
- The risks of VTE with CHCs and reduced bone mineral density with DMPA in PwMS
- Emergency contraception in this patient population

Further research is also needed on the teratogenic risks associated with the use of certain DMTs in men, particularly as advice on the use of contraceptive methods differs in the product labeling across countries.

The faculty commented that CHC or progestin-only contraception use for the regulation of MS symptoms reflects inter-patient variation, so should be individualized and may not be evidence-based. HCPs should refer to the Faculty of Sexual and Reproductive Healthcare guidelines and approved contraceptive labels,^{12,14} and contraceptive devices, such as the IUD or patch, may be considered.

The SC agreed that family planning should be discussed with PwMS. Conversations regarding contraception must be handled sensitively, be driven by the patient, and include partners, depending on patient preference. A balanced discussion should be undertaken covering the risk–benefit of all contraceptive methods, and patients should not feel restricted in their choice. Contraceptive coercion should be avoided and the patient's preferred method of contraception always considered. As most female PwMS are diagnosed during their childbearing years, these conversations are particularly relevant and disease stabilization before a planned pregnancy is recommended. All PwMS should be made aware of the risks with DMT use and the effect of pregnancy on MS, particularly postpartum.^{3,6} Experts agreed that patients should make the final decision and they need to feel comfortable with their chosen method of contraception, proceeding with caution in some instances.

The SC highlighted that certain DMT labels may be overly conservative and inconsistent, and noted that European Medicines Agency (EMA) and Food and Drug Administration guidelines may differ for the same product, for example, ocrelizumab.^{36,37} The SC also noted that not all labels reflect real-world practice; therefore, expert opinion and additional data for DMT use in pregnancy should be considered. For example, the EMA suggests waiting 12 months from last ocrelizumab infusion before pregnancy, but data and expert opinion support a much shorter time.³⁶ Off-label advice may also be considered at the judgment of the clinical team, but HCPs must be aware of the legal landscape in their jurisdiction regarding off-label use. This should be openly discussed with the patient and their family, if desired by the patient, and all discussions documented. Key factors to consider when prescribing DMTs to WOCBP are disease control, the potential to cause fetal harm, and if the DMT will be used long term, irrespective of the fact that it may be teratogenic or gonadotoxic. PwMS should remain on their current non-teratogenic DMT until conception and the risk of an MS relapse should be balanced against the potential risk to the embryo/fetus. When prescribing a DMT that may be present in semen to male PwMS, it is important to provide guidance on effective contraception to prevent transference of the active substance to a female partner. Barrier contraceptives, such as condoms, are recommended, although erectile dysfunction should be considered when providing this advice. It is important to emphasize that fertility awareness-based contraceptive methods are generally not recommended for PwMS receiving teratogenic/gonadotoxic medications as the risk of failure/pregnancy is high.

It was reflected in the voting and comments that some neurologists feel they do not have the necessary knowledge of contraception to support patients' decisions; therefore, education is recommended if required. Most contraceptive advice does not require advanced specialist knowledge. It may be beneficial to refer to the medical eligibility criteria when discussing contraception to highlight any contraindications, for example, migraines with aura symptoms. Another key consideration is time constraints; in cases where specialist advice is required, it may not be possible to have comprehensive MDT discussions with patients.

Conclusion

These consensus-based clinical recommendations represent the opinions and perspectives of 44 international clinical experts and are based on current evidence. Joining other consensus recommendations

around reproductive health and MS,^{6,9,15,19,32} namely evolving guidelines for MS treatment during pregnancy and for family planning and pregnancy in PwMS,^{6,9,15} the current recommendations provide the first specific guidance around the most important aspects of contraception for PwMS.

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Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

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Supplemental Material

Supplemental material for this article is available online.

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