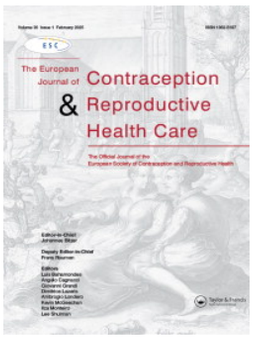

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REVIEW ARTICLE

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Family planning and contraception in people with multiple sclerosis: perspectives for obstetricians, gynaecologists, and other health care professionals involved in reproductive planning

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ABSTRACT

Purpose: Multiple sclerosis (MS) is often diagnosed in people of reproductive age. However, family planning counselling is not always integrated within MS care. Decisions on family planning can be further complicated by potential side effects associated with several disease-modifying therapies. While neurologists may lack training in contraceptive use and family planning counselling, obstetricians and gynaecologists (OB-GYNs) and other health care professionals involved in reproductive life planning (RHCPs) may lack detailed knowledge and experience around the use of contemporary MS treatments.

Material and methods: Through a modified Delphi consensus programme, a multidisciplinary steering committee of 13 international experts developed practical clinical recommendations on contraceptive use and family planning for people with MS (PwMS). This article offers insights to help OB-GYNs and RHCPs implement these recommendations, focusing on contraceptive decision-making and MS medications.

Results: The perspectives discussed emphasise providing education on MS to OB-GYNs and other RHCPs, enabling informed counselling for PwMS and their partners regarding contraception and family planning. Close collaboration among the multidisciplinary team, including neurologists, is crucial in providing reproductive care for PwMS.

Conclusions: The detailed perspectives provided aim to enable OB-GYNs and other RHCPs to provide informed counselling for PwMS and their partners regarding contraception and family planning.

SHORT CONDENSATION

Multiple sclerosis (MS) onset often coincides with reproductive age, but family planning counselling is not standard in MS care. The detailed perspectives provided here aim to enable health care professionals involved in reproductive life planning to provide informed counselling for people with MS and their partners.

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Multiple sclerosis; contraception; disease-modifying therapy; expert opinion; gynaecologist; obstetrician; neurologist

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating neurodegenerative disease involving the central nervous system (CNS) [1]. The symptoms of MS arise from an inflammatory-based myelin disruption within the CNS initiated by activated immune cells [2]. Symptoms can be unpredictable and vary greatly among patients and over time [2], including observable deficits in strength, mobility, balance, and vision, and more 'invisible' symptoms such as dizziness, fatigue, cognitive fog, depression, anxiety, and genitourinary dysfunction [2–4]. People with MS (PwMS) report a considerable detrimental impact on daily activities and health-related quality of life [5–7].

Disease activity in MS is thought to reflect inflammatory processes causing focal lesions in the brain and spinal cord,

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with dysfunction of the blood–brain barrier [8, 9], and is defined as relapses and/or evidence of new magnetic resonance imaging activity over a specified period of time [10]. Disease progression is thought to reflect neurodegenerative processes and/or compartmentalised chronic inflammation, and is defined as a confirmed increase in disability following a relapse without unequivocal recovery or progression independent of relapse activity (PIRA) [8, 11, 12].

Disease-modifying therapies (DMTs) are available for patients with MS, which reduce immune attacks on the CNS [13]. There are numerous DMTs and they have different modes of action, routes of administration, dosing regimens, efficacy, tolerability, and/or contraindications [14, 15].

The worldwide prevalence of MS is increasing, with an estimated ~2.8 million people affected in 2020 [16]. Women are ~3–4 times more frequently affected than men [16–19]. The clinical onset and the diagnosis of MS generally occur during the reproductive years [16]; thus, dedicated family planning counselling is often required. Several DMTs are generally not recommended for women trying to conceive owing to potential risks to the fetus [20]. Effective contraceptive methods are advised and washout periods are essential for certain DMTs prior to conception [21]. Between 2006 and 2016, the overall proportion of pregnancies conceived in PwMS while on DMTs increased [22], suggesting that, if counselling on contraception/family planning and the teratogenic effects of DMTs is occurring, counselling needs to be more effective. Furthermore, in an online survey in Denmark of 590 PwMS, 42% of female respondents reported that they 'did not know' when asked about their knowledge of teratogenic risks related to DMTs, revealing a knowledge gap among many patients [23].

Neurologists may have insufficient knowledge and experience regarding the best reproductive health practices for the management of PwMS [24], while obstetricians and gynaecologists (OB-GYNs) and other health care professionals involved in reproductive life planning (RHCPs) may lack knowledge and experience in MS, particularly specifics around DMT contraindications and how these may influence decisions relating to contraception and pregnancy [24]. Additionally, there is currently a lack of comprehensive guidance for daily practice on family/reproductive life planning for PwMS. To address these gaps, a consensus-based programme was conducted to provide expert-led, consensus-based, practical recommendations on contraceptive use and family/reproductive life planning for PwMS [25]. This manuscript aims to offer practical guidance on the most appropriate contraceptive methods for PwMS, considering key factors such as reproductive life planning, contraceptive decision-making, and the effects of MS medications.

Materials and methods

A multidisciplinary steering committee (SC) of 13 international HCPs developed 15 key clinical questions and 25 recommendations on contraception in PwMS using evidence from a systematic literature review and expert opinions from the SC [25]. Consensus was achieved on 24 out of 25 clinical recommendations following voting by 12 SC members and a further 32 extended faculty members. The full methodology of the consensus-based programme and the final recommendations have been published [25].

OB-GYNs from the SC identified themes and recommendations from the consensus programme that they felt were most relevant to their community and clinical practice. With the support of the wider SC, the objective was to deliver broader education on MS for OB-GYNs and other RHCPs (e.g. nurses, midwives, and primary care physicians) through the provision of pertinent information to aid the implementation of this practical guidance into real-world clinical practice, addressing known educational needs. The consensus results and perspectives described here were presented at the 19th World Congress on Human Reproduction in Venice, Italy, March 15–18, 2023 [26].

Here, we focus on three themes: 1. Reproductive life planning, 2. contraceptive decision-making, and 3. MS medications.

Results[1]

Reproductive life planning for PwMS

When PwMS seek information regarding reproductive life planning and contraception, it is important, when feasible, that OB-GYNs engage as part of the multidisciplinary team that informs and provides guidance. The multidisciplinary team may also include endocrinologists, general practitioners, clinical nurse specialists, midwives, pharmacists, and social workers [25, 27–29]. In particular, OB-GYNs and neurologists need to collaborate when providing reproductive care for PwMS [28, 30]. MS nurses are actively involved in counselling women planning reproductive life to make informed choices about their treatment options. PwMS and their partners should receive tailored reproductive life planning counselling at diagnosis, before starting MS treatment, and at regular follow-ups [25]. Topics for discussion during dedicated, tailored family planning counselling for PwMS (Figure 1) include: the potential risks or impact of certain DMTs on unplanned pregnancies (e.g. potential teratogenic effects; discussed further in the *MS medications* section); the effectiveness and risk–benefit profile of different contraceptive options; and, in patients who wish to conceive, the importance of planning their desired pregnancy around the choice/dose/timing/switching/stopping of their DMT (if possible).

Contraceptive decision-making for PwMS

It is important that PwMS can make informed, individualised decisions around reproductive life planning and contraceptive use, ensuring their personal autonomy is respected throughout the decision-making process [31] (Figure 2). In this regard, a balanced counselling strategy can be effective in some clinical settings [32–34] and should be considered, although other counselling approaches are also valuable.

Contraceptive-related factors

Data are limited comparing the safety and efficacy of different contraceptive products (e.g. synthetic estrogens vs natural estrogens or different progestogens), dosages, and routes of administration (e.g. oral, transdermal, intravaginal, subcutaneous, intramuscular, intrauterine); therefore,

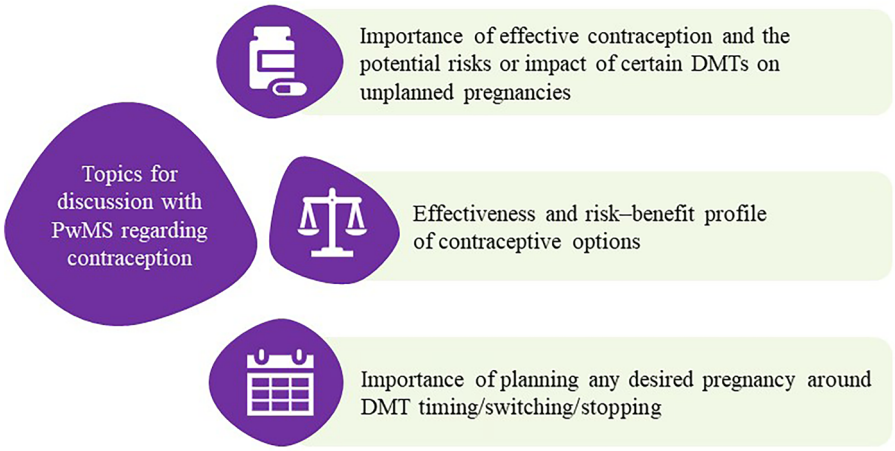

Figure 1. Contraception topics for discussion during dedicated reproductive life planning counselling for PwMS. DMT, disease-modifying therapy; PwMS, people with multiple sclerosis.

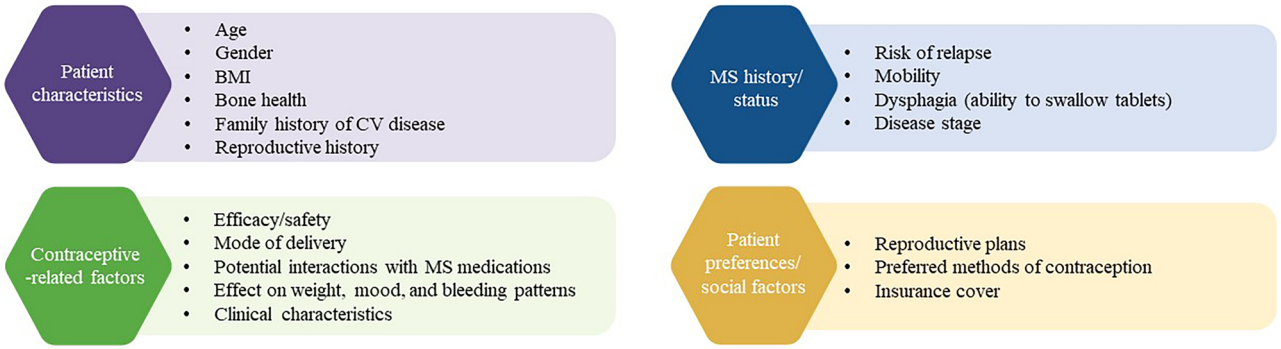

Figure 2. Influencing factors for contraceptive decision-making by PwMS (includes *biological sex* [males and females] and *gender identity* [cisgender and transgender individuals]). BMI, body mass index; CV, cardiovascular; MS, multiple sclerosis; PwMS, people with multiple sclerosis.

the clinical characteristics of each product should be considered. Contraceptive-related factors that may influence the decision-making of PwMS include the efficacy of the contraceptive being discussed, any contraindications, and the potential risks, such as cardiovascular (CV) adverse events and interactions with any medications (for MS or otherwise) patients may be taking [25]. Some contraceptive methods are associated with side effects that may be perceived as intolerable and these should be highlighted during the decision-making process. For example, while there are significant benefits to long-acting reversible contraceptives (LARCs), such as exceptional efficacy, certain side effects, such as abnormal uterine bleeding and impacts on mood or weight [35], may not be acceptable for some women. Furthermore, depression and sexual dysfunction are frequently reported in PwMS [36, 37]; therefore, contraceptive methods that could worsen these symptoms may not be tolerated. While some side effects may be directly related to contraceptives, the incidence may vary widely among individuals.

Patient-related factors

Patient characteristics (e.g. age, biological sex, gender identity, body mass index), MS history/status (e.g. risk of relapse, disability, mobility issues, ability to swallow tablets, and disease stage), and medical history (e.g. bone health, family history of CV disease, gynaecologic history, comorbidities, and current medications) should be considered when making decisions on contraception. Counselling should centre on the individuals' contraceptive preferences [31], incorporating information on relevant insurance coverage and future reproductive plans. PwMS should be counselled regarding the benefits and risks of various forms of contraception, taking into account their age, risk factors and comorbidities, and severity of MS. Certain factors associated with MS may influence their suitability for certain contraceptives (Figure 3).

Combined hormonal contraceptives (CHCs) have been associated with increased risk of blood clots and, therefore, are not recommended for women of childbearing potential with MS with a significant risk of venous thromboembolism (VTE), mobility issues, or high levels of disability [28, 38, 39]; for these patients, a LARC or progestin-only pill would be more appropriate. Although natural estrogens are biologically plausible as having thrombotic risk [40], further confirmation is needed to substantiate this in clinical practice. Large randomised controlled trials have shown that CHCs and estriol have modest effects on reducing inflammatory activity, with estriol also showing potential neuroprotective benefits [41]. However, observational studies indicate that CHCs offer no clear protection against MS-related inflammatory activity [41]. These findings underscore the need for more in-depth research to guide HCPs in making evidence-based decisions about CHC use in women with MS.

It is also important for OB-GYNs and other RHCPs to refer to, and become familiar with, medical eligibility criteria as there are various contraindications associated with CHCs, not just limited to VTE; for example, lupus

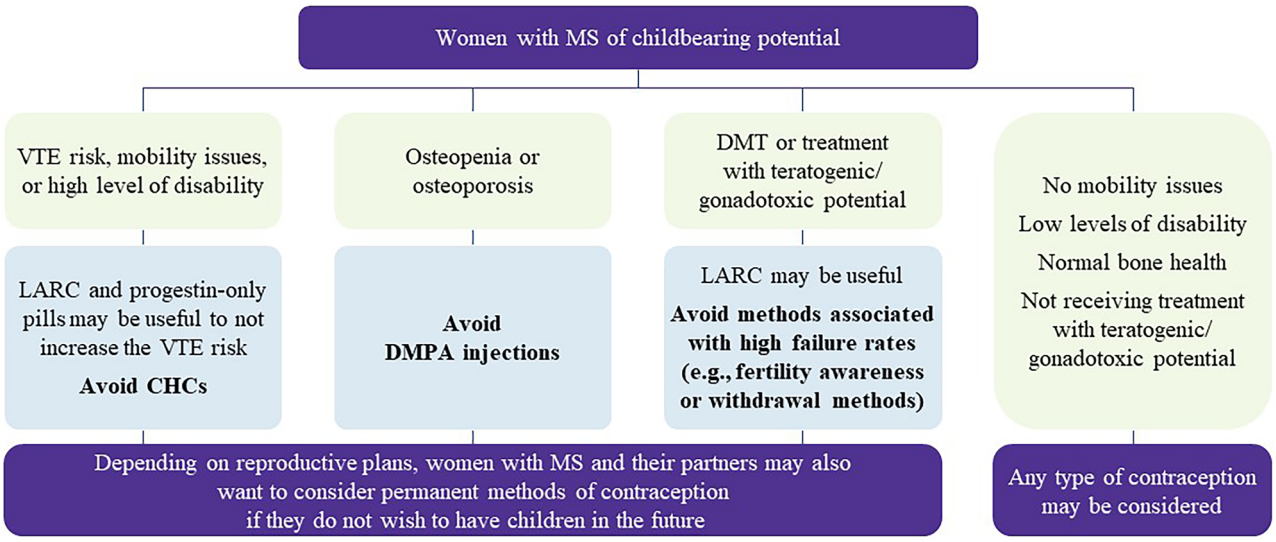

Figure 3. Algorithm of contraception considerations for PwMS. CHC, combined hormonal contraceptive; DMPA, depot medroxyprogesterone acetate; DMT, disease-modifying therapy; LARC, long-acting reversible contraceptive; MS, multiple sclerosis; PwMS, people with multiple sclerosis; VTE, venous thromboembolism.

with antiphospholipid antibodies, smoking over the age of 35 years, and migraines with aura. The European Society for Contraception and Reproductive Health provides teaching and training on such medical issues, among many other related topics [42]. Furthermore, the US Selected Practice Recommendations state that no regular follow-up is required upon initiation of CHCs [31], but recommend monitoring blood pressure and discussing with the patient during routine health care visits their satisfaction and any potential concerns with the contraceptive method [31]. These general recommendations may vary for different populations. Specific populations, such as PwMS, might benefit from more frequent follow-up visits in specialist centres to assess any changes in health status that would impact the appropriateness of CHCs for safe and effective continued use, such as ensuring that patients have not developed any contraindications, or have not switched MS medications.

With progestin-only contraceptives, such as the progestin-only pill, implant, or injectable (see Table 1 for a summary), the type of progestin may not be considered as they often work in a similar manner and have limited variability. However, depot medroxyprogesterone acetate (DMPA) may have a negative impact on bone density in some young women still developing peak bone density [28, 68]; although, in women aged 30–45 years, studies found that bone density is maintained over time with DMPA [69, 70]. In most affected women, any loss of bone mineral density is recovered upon discontinuation [71]. PwMS should be educated on the associated potential risks with DMPA as they age; indeed DMPA may not be suitable for patients with bone mineral density concerns, osteoporosis, or osteopenia (Figure 3). However, its use should not be restricted if PwMS want to proceed with DMPA injections as their form of contraception [28, 68].

LARCs include intrauterine devices (IUDs; hormonal and non-hormonal) and hormonal implants (see Table 1 for a summary). All are highly effective as contraceptive methods but differ in the mode of administration, mechanism of action, and associated side effects [67, 72, 73]. While there are a few contraindications for LARCs, the copper IUD may be the method of choice for women who want to avoid the use of hormonal methods, while an levonorgestrel intrauterine system may be more suitable for women with long, painful, and heavy periods [72].

An important factor to consider during the decision-making process is the prescribed MS medication(s). Generally, in patients receiving DMTs associated with potential teratogenic effects, fertility awareness methods or withdrawal methods of contraception are not recommended (Figure 3) [25, 74]. A discussion may include their comfort level with a particular method, taking into consideration their socio-cultural environment and choice, and whether they would continue with an unplanned pregnancy. If PwMS decide to choose a fertility awareness method after receiving advice to the contrary, they should still be educated on how to optimise the method (e.g. avoiding intercourse during their fertile window) while informing them of the high failure rates.

If they do not wish to have children or to add to their existing family, PwMS and their partners may also consider permanent methods of contraception, such as vasectomy in males or tubal ligation in females.

MS medications

DMTs

A key consideration for PwMS of reproductive age is the long-term effects of MS treatment (DMTs and symptomatic medications) on an embryo/fetus.

Current pharmacotherapy for MS involves DMTs that modify the course of the disease through suppression or modulation of immune functions. DMTs are often prescribed by neurologists specialised in MS early in the disease course to prevent later disability [75, 76]. High-efficacy DMTs provide near-complete control of relapsing MS and focal CNS inflammation, with a greater likelihood of patients living a disability-free life [76].

The most commonly used DMTs for relapsing–remitting MS (RRMS) are shown in Table 2; these include interferon β (IFN β), glatiramer acetate, teriflunomide, ofatumumab, dimethyl fumarate, fingolimod, ponesimod, ozanimod,

Table 1. Summary of progestin-only and LARC contraceptive options.

Method	Effectiveness and need for back up	Most common AEs (this list is not exhausted)
Progestin-only contraceptives		
Progestin-only pill[a]		
Desogestrel	• Approximately 0.3/100 women per year using progestin-only pills become pregnant with consistent and correct use [43] • Effective if taken on the first day of bleeding [44] • Starting on days 2–5 is allowed, but during the first cycle a barrier method is recommended for the first 7 days of tablet-taking [44]	≥1% [44]: • Mood altered, depressed mood • Decreased libido • Headache • Nausea • Acne • Breast pain • Irregular menstruation, amenorrhoea • Weight increase
Norethisterone	• Approximately 0.3/100 progestin-only pills users become pregnant with consistent and correct use [43] • Effective if taken on the first day of bleeding [45, 46] • Additional barrier method is recommended for the first 7 days of taking the tablets [45]	Common AEs [45, 46] • Menstrual irregularity [85] /cycle irregularity during the first few months of therapy [45] • Spotting or breakthrough bleeding [45] • Amenorrhoea [45] • Breast discomfort [45], breast tenderness [46] • Gastrointestinal symptoms [45], nausea [46] • Rash [45] • Headaches [45, 46] or migraine [45] • Dizziness [46] • Depression [45] • Fatigue [45] • Nervousness [45] • Disturbance of appetite and changes in weight [45] • Hepatic adenoma [45] • Libido [45]
Progestin-only injectables		
DMPA—releases **medroxyprogesterone acetate**, a first-generation progestin [47,48]	• Approximately 0.2/100 women per year using DMPA become pregnant in the first year with consistent and correct use [43] • Effective for at least 12 weeks [47] • Effective after first injection for contraception if injected within the first 5 days of a period [47, 48] • Return to ovulation is expected for most women within 12 months of the last infection [47, 48]	• Nervousness [47] • Headache (>5% [48] or >10% [47]) • Abdominal pain, discomfort (≥10%) [47] • Increased weight (>5% [48] or >10% [47]) • Dysfunctional uterine bleeding (>5%) [48] • Amenorrhoea (>5%) [48] • Injection site reactions (>5%) [48]
LARCs		
IUDs—non-hormonal copper IUDs		
Copper IUDs (with plastic frame; containing various amounts of copper) [49][b]	• 0.6/100 women per year using copper IUD become pregnant with consistent and correct use [43] • Highly effective; 5-year gross failure rates: <1% [50, 51] • 5–10 years of contraceptive efficacy [50]	• Lack of systemic side effects [50][c] • During and after insertion [50]:[c] ◦ Vasovagal syncope (very rare) ◦ Cramping for several days ◦ Spotting for a few weeks • Long term [50]:[c] ◦ Longer and heavier periods ◦ Bleeding or spotting between periods ◦ Dysmenorrhoea ◦ Rarely iron deficiency over many years
IUDs—hormonal IUS		
LNG-IUSs (with plastic frame, different sizes, containing different amounts of LNG) [49]	• 0.5/100 women per year using LNG-IUS become pregnant with consistent and correct use [43]	
LNG 20 IUS/LNG-52 IUS	• Highly effective; 8 years of contraceptive efficacy [52, 53]	≥10%: • Uterine/vaginal bleeding (spotting, oligomenorrhoea, amenorrhoea) [52] • Alterations of menstrual bleeding patterns [53] • Abdominal/pelvic pain [53] • Headache/migraine [53] • Genital discharge [53] • Vulvovaginitis [53] • Ovarian cysts [54]
LNG 16 IUS/LNG 19.5 mg	• 5 years of contraceptive efficacy [55, 56]	≥5%: • Headache [55, 56] /migraine [55] • Abdominal/pelvic pain [55, 56] • Acne/seborrhoea [56] • Bleeding changes including increased [55, 56] / decreased menstrual bleeding, spotting, infrequent bleeding and amenorrhoea [56] • Ovarian cyst [55, 56] • Vulvovaginitis [55, 56] • Dysmenorrhoea/uterine spasm [55] • Breast pain/breast discomfort [55]

(*Continued*)

Table 1. Continued.

Method	Effectiveness and need for back up	Most common AEs (this list is not exhausted)
LNG12 IUS/LNG 13.5 mg	• 3 years of contraceptive efficacy [57, 58]	≥10%: • Headache [57, 58] /migraine [57] • Abdominal/pelvic pain [57, 58] • Acne/seborrhoea [57, 58] • Bleeding changes, including increased/decreased menstrual bleeding, spotting, infrequent bleeding and amenorrhoea [57, 58] • Ovarian cyst [57, 58] • Vulvovaginitis [57, 58] • Dysmenorrhoea/uterine spasm [57]
Contraceptive implants		
Contraceptive implants (small plastic devices placed under the skin in the upper arm that release **etonogestrel**, a third-generation progestin [59–61]	• 0.1/100 women per year using contraceptive implants become pregnant with consistent and correct use [43] • Highly effective; 3 years of contraception efficacy [60, 61] • Effective for contraception if inserted within 5 days of bleeding. If inserted as recommended, no backup contraception is necessary [60, 61] • If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion [60, 61]	≥10%: • Vaginal infection/vaginitis [60, 61] • Headache [60, 61] • Acne [60, 61] • Breast tenderness or pain [60, 61] • Irregular bleeding [60] /change in menstrual bleeding pattern [61] • Weight increase [60, 61] • Abdominal pain [61] • Pharyngitis [61]

Further research is needed to differentiate the effects of CHCs in MS, particularly focusing on the role of different estrogens and their specific impacts on the disease.

[a]Note: This table does not offer an exhaustive compilation of all approved progestin-only pills. For a thorough inventory, refer to the EMA (https://www.ema.europa.eu/en/homepage), FDA (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm), or your local regulatory authority website.

[b]Supported by numerous studies worldwide [62–65].

[c]Based on a study that examined 545 case notes of patients having IUD insertions at East Cheshire NHS Trust family planning clinics between 1 October 1997 and 31 December 2000 [66].

LARCs are safe while breastfeeding, can be placed shortly after giving birth, and are removable. Pregnancy is possible immediately following removal [67].

AE, adverse effect; CHC, combined hormonal contraceptive; DMPA, depot medroxyprogesterone acetate; EMA, European Medicines Agency; FDA, Food and Drug Administration; IUD, intrauterine device; IUS, intrauterine system; LARC, long-acting reversible contraception; LNG, levonorgestrel; MS, multiple sclerosis; NHS, National Health Service.

cladribine tablets, ocrelizumab, ublituximab, rituximab (used off-label), alemtuzumab, and natalizumab. It is recommended that HCPs involved in counselling PwMS stay updated on MS medications.

Effects of DMTs on fetal development and pregnancy

For most DMTs, there are few data available on the effects of a given medicine on fetal development and pregnancy, with the exception of the IFNs, glatiramer acetate, fingolimod, dimethyl fumarate, natalizumab, and ocrelizumab. Results from the European IFN β Pregnancy Registry found no evidence that IFN β exposure before conception and/or during pregnancy adversely increases the rate of congenital anomalies or spontaneous abortions in an analysis of data from 948 pregnancy reports [124]. Similar results were observed in a large cohort-based study of 797 IFN β–exposed pregnancies in women with MS in Finland and Sweden [125]. In an analysis of >5,000 pregnancies during which women with MS were exposed to branded glatiramer acetate, there was no observed increased risk of congenital anomalies, compared with that reported by the European Surveillance of Congenital Anomalies and the Metropolitan Atlanta Congenital Defects Program (MACDP) [126]. Safety data from real-world studies showed that rates of miscarriage in women with MS treated with natalizumab are similar to the general population, while rates of congenital malformations are slightly higher but not directly linked to treatment [127, 128]. In an observational, retrospective analysis of six patients with highly active MS who unexpectedly became pregnant while undergoing natalizumab treatment and chose to continue the therapy via an extended 6-week interval dosing schedule under the clinical practice protocol (NAP-30), none of the babies developed congenital malformations, birth defects, or developmental disorders, with follow-up periods ranging from 6 to 32 months [129]. As a result of these and other studies, there is no advice on a need for contraception provided in the EU and US labels for IFNs [77–79, 81–83], glatiramer acetate [87–89], and natalizumab [115,116] (Table 2). Furthermore, there is no requirement for a washout period prior to pregnancy for these medications. IFNs may be considered if clinically needed [77–79, 81–83] and as a precautionary measure; it is preferable to avoid the use of glatiramer acetate during pregnancy unless the benefit to the mother outweighs the risk to the fetus [87, 88]. Natalizumab should only be considered if the benefit to the mother outweighs the risk to the fetus, taking into account the patient's clinical condition and the possible return of disease activity after stopping [115]. Overall, for PwMS who become pregnant while on IFNs, glatiramer acetate, or natalizumab, the decision to continue, switch, or discontinue treatment should be individualised based on their clinical history and disease activity. Importantly, discontinuing natalizumab and sphingosine-1-phosphate receptor modulators without using a bridging therapy prior to pregnancy exposes patients to a significant risk, not just of MS reactivation, but of severe rebound disease activity [130, 131]. Contraceptive measures and washout periods prior to pregnancy are recommended in Table 2.

Analyses of clinical trial data, post-marketing surveillance studies, and pregnancy registries following outcomes in neonates exposed to DMTs in utero and through breastfeeding are ongoing. Recent study results, where available, are summarised in Table 3. As increasing data are generated in this field, more individualised treatment decisions will be enabled, which is particularly important for women

Table 2. Key characteristics of commonly used DMTs for the treatment of RRMS, including considerations for contraception and pregnancy.

DMT[a]	Contraception advised in the current label	Medication half-life[b]	Washout prior to pregnancy recommended according to SmPC/US label/practical recommendation	Additional relevant information from the label
Injectables				
Immunomodulation (interferon)				
IFN β-1a [77–80] **IFN β-1b** [81–83] **pegIFN β-1a** [84, 85]	No	**IFN β-1a:** ~10 hr (IM); ~50–70 hr (SC) **IFN β-1b**: 5 hr (SC) **pegIFN β-1a:** ~78 hr (SC)	Discontinuation may not be recommended before completion of pregnancy testing Premedication with ibuprofen should not be taken after 28 weeks of gestation due to premature closure of the ductus arteriosus; an alternative is paracetamol [86]	No increased risk of major congenital anomalies after preconception exposure to IFN β or such exposure during the first trimester of pregnancy
Immunomodulation (synthetic amino acid polymer)				
Glatiramer acetate [87–89]	No	NA (SC)	Additional contraception is not needed	Available human data in pregnant women are not sufficient to make conclusions about the potential risks on birth defects and miscarriage
B-cell depletion therapy				
Ofatumumab [90, 91]	Yes	16 days (SC)	Yes, contraception should be continued for 6 months after the last dose Can be used until the completion of pregnancy testing Contraindicated during pregnancy	Limited amount of data from the use of ofatumumab in pregnant women. Ofatumumab may cross the placenta and cause fetal B-cell depletion
Oral				
Immunomodulation (dihydroorotate dehydrogenase inhibition)				
Teriflunomide [92, 93]	Yes	~19 days (median)	Yes. For women who wish to become pregnant, teriflunomide should be stopped 24 months before conception [86]. An accelerated elimination procedure is recommended to more rapidly achieve concentrations <0.02 mg/l Contraindicated during pregnancy	If an accelerated elimination procedure is not used, teriflunomide plasma levels can be >0.02 mg/l for an average of 8 months. However, in some patients, it may take up to 2 years to reach a plasma concentration below 0.02 mg/l Contraceptive use is recommended for men to minimise any potential risk
Anti-lymphocyte trafficking (S1P receptor modulation)				
Fingolimod [94, 95]	Yes	6–9 days	Yes, contraception should be continued for 2 months after treatment discontinuation Contraindicated during pregnancy	Data suggest that use of fingolimod is associated with an increased risk of major congenital malformations when administered during pregnancy compared with the rate observed in the general population
Ponesimod [96, 97]	Yes	33 hr (IV)	Yes, contraception should be continued for 1 week after treatment discontinuation	No data on the use of ponesimod in pregnant women, but studies in animals have shown reproductive toxicity
Ozanimod [98, 99]	Yes	~21 hr	Yes, contraception should be continued for 3 months after treatment discontinuation	No/limited amount of data available in pregnant women. Studies in animals have shown reproductive toxicity, including fetal loss and anomalies, notably malformations of blood vessels, generalised oedema, and malpositioned testes and vertebrae
Siponimod[d] [100, 101]	Yes	~30 hr	Yes, contraception should be continued for at least 10 days after stopping treatment	No/limited amount of data available in pregnant women, but animal studies have shown embryotoxicity, fetotoxicity, and teratogenicity
Immunomodulation				
Dimethyl fumarate[a] [102, 103]	Yes	Active metabolite monomethyl fumarate: ~1 hr	Contraindicated during pregnancy	Interim results from a large registry indicate that the use of dimethyl fumarate in pregnant women in the first trimester is not significantly associated with adverse pregnancy outcomes [104], but animal studies have shown reproductive toxicity
Immune reconstitution (synthetic deoxyadenosine analogue)				
Cladribine tablets [105, 106]	Yes, in men and women	~1 day	Yes, contraception should be continued for at least 6 months after the last dose Contraindicated during pregnancy Cladribine is not expected to decrease the efficacy of hormonal contraceptives (ethinylestradiol and levonorgestrel). Therefore, double contraception (hormonal and barrier methods) are no longer recommended	As cladribine interferes with DNA synthesis, adverse effects on human gametogenesis could be expected and male patients must take precautions to prevent pregnancy of their partner during cladribine treatment and for at least 6 months after the last dose
Infusion				
Immune reconstitution (lymphocyte depletion via anti-CD52 antibody)				
Alemtuzumab [107, 108]	Yes	4–15 days	Yes, contraception should be continued for 4 months after each course of treatment Contraindicated during pregnancy	Limited amount of data on using alemtuzumab in pregnant women. Placental transfer and potential pharmacologic activity were observed in mice. Animal studies have shown reproductive toxicity

(*Continued*)

Table 2. Continued.

DMT[a]	Contraception advised in the current label	Medication half-life[b]	Washout prior to pregnancy recommended according to SmPC/US label/practical recommendation	Additional relevant information from the label
B-cell depletion therapy (anti-CD20 antibody)				
Ocrelizumab [109, 110]	Yes	26 days	Yes, contraception should be continued for 6 (USA) or 12 (Europe) months after the last infusion	Limited amount of data on using ocrelizumab in pregnant women. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy
Ublituximab[e] [111, 112]	Yes	22 days	Yes, contraception should be continued for at least 4 months after last infusion	Limited amount of data in pregnant women. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy
Rituximab[f] [113, 114]	Yes	22 days (median)	Yes, contraception should be continued for 12 months after the last infusion	No adequate and well-controlled data from studies in pregnant women, but transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. Similar effects have been observed in animal studies
Anti-lymphocyte trafficking (anti-α4-integrin antibody)				
Natalizumab [115, 116]	No	28.2 days (median; IV)	No, but it may be recommended to discontinue during pregnancy[c]	Data from clinical trials, a prospective pregnancy registry, post-marketing cases, and available literature do not suggest an effect of natalizumab exposure on pregnancy outcomes Thrombocytopenia and anaemia in the post-marketing setting have been reported

Within each category, the DMTs are colour coded for efficacy according to how effectively they reduce the MS relapse rate based on broad categories recommended in guidelines published by the ABN (yellow = moderately effective – reduces relapses by 30%; grey = more effective than yellow - reduces relapses by 50%; orange = highly effective – reduces relapses by 70%) [14, 117]. DMTs that are not colour coded have not been categorised according to this criterion by the ABN.

[a]None of the below drugs have been found to interfere with oral contraceptives. However, dimethyl fumarate may cause gastrointestinal side effects within the first few weeks of treatment [118] and, therefore, could reduce oral contraceptive efficacy. Additional contraceptive measures are advisable in case of interference with absorption of the contraceptive pill/oral contraceptives (both combined estrogen and progesterone, and progesterone-only pill).

[b]Plasma drug concentration declines by 50% during each half-life so that very little of a bolus dose remains after four or five half-lives [119].

[c]Decision will include an assessment of whether the benefit of relapse prevention to the mother outweighs the risk to the fetus.

[d]In clinical studies, siponimod reduced the risk of disability progression by 37% in people with secondary progressive MS [14].

[e]In large clinical studies, ublituximab reduced the relapse rate by over 50% compared with teriflunomide [14].

[f]Rituximab is used off-label for the treatment of MS [120]. The label for rituximab reflects its approved indications (e.g. certain types of lymphoma, rheumatoid arthritis, and other autoimmune conditions), and does not include the most up-to-date evidence from research on its effectiveness and safety in MS [121–123].

For all products, registries are ongoing that follow outcomes in DMT-exposed pregnancies. Information taken from relevant product labels, correct as of December 2023. Please refer to most recent local product labels for up-to-date information.

ABN, Association of British Neurologists; CD, cluster of differentiation; DMT, disease-modifying therapy; hr, hour; IFN, interferon; IM, intramuscular; IV, intravenous; MS, multiple sclerosis; NA, not available; pegIFN, pegylated interferon; RRMS, relapsing-remitting MS; S1P, sphingosine-1-phosphate; SC, subcutaneous; SmPC, summary of product characteristics.

with high disease activity or who are treated with DMTs associated with risk of discontinuation rebound.

Limited or inconclusive data exist regarding the impact of certain DMTs, such as glatiramer acetate, cyclophosphamide, azathioprine, and methotrexate, on male reproduction, including effects on spermatogenesis and the risk of gonadotoxic/teratogenic outcomes, with a significant lack of information for most DMTs [139] (Table 2). Male contraception is required during cladribine treatment and for 6 months after the last dose, as it may interfere with DNA synthesis [105, 106, 140], and during teriflunomide treatment when planning to conceive, as the drug is present in semen (although human fertility data are lacking) [92].

DMT washout periods

The optimum washout period after discontinuing a DMT, before attempting to conceive, differs depending on the type of DMT (Table 2). Effective contraception should be used during this time until the washout period is complete. Following discontinuation of teriflunomide, contraception should be used until plasma levels reach <0.02 mg/l [92, 93]. This takes an average of 8 months, although it may take up to 2 years in some patients [92, 93]. Therefore, an accelerated elimination procedure is recommended using either cholestyramine 8 g three-times daily for 11 days or 50 g of activated powdered charcoal every 12 h for 11 days [92, 93]. The washout periods recommended in the EU labels range from 1 week for ponesimod to 12 months for ocrelizumab. However, this guidance is not always based on physiological principles or available data, and real-world practice may differ considerably [86, 141–143]. Clinicians must make informed, evidence-based decisions that prioritise patient outcomes, recognising that regulatory guidelines may not always reflect the latest evidence.

Discussion

In this article, we have focused on three key themes most relevant to the OB-GYN community: family/reproductive life planning, contraceptive decision-making, and MS medications. Broad education has been provided on MS for OB-GYNs and other RHCPs, in addition to guidance that can be implemented into clinical practice, addressing known educational needs.

Family planning counselling is not currently part of standard MS care, despite its importance. Without proper

Table 3. Summary of available pregnancy registry information for MS DMTs requiring washout.

DMT	Source of information	Number of pregnancies (N)	Outcomes
Injectables			
Ofatumumab	Novartis Safety Database analysis [104]	32 • Exposure to ofatumumab after LMP, *n* = 12 • Exposure within 6 months prior to LMP, *n* = 4 • Exposure timing unknown, *n* = 16	As of August 2021: • Known outcomes, *n* = 23: ◦ Spontaneous abortion, *n* = 6 ◦ Therapeutic/induced abortion, *n* = 6 ◦ Live births, *n* = 11 ◦ No congenital anomalies and no reports of B-cell depletion, immunoglobulin/haematologic/fetal abnormalities, and no serious infections were reported in the babies • Unknown outcomes, *n* = 4 • Outcome pending, *n* = 5
Oral			
Teriflunomide	Clinical trials and post-marketing surveillance - Sanofi Global Pharmacovigilance Database [132]	437 • From clinical trials, *n* = 70 • From post-marketing setting, *n* = 367	As of December 2017: • Known outcomes, *n* = 222: ◦ Spontaneous abortions, *n* = 47 ◦ Elective abortions, *n* = 63 ◦ Live births, *n* = 107 ◦ Ectopic pregnancies, *n* = 3 ◦ Stillbirth, *n* = 1 ◦ Maternal death, *n* = 1 • Included four birth defects (one of which was considered major)
Fingolimod	Novartis Safety Database analysis [133]	1,246 (1,255 infants); of these, 113 from registry and 674 from PRIM study • Exposure within 8 weeks of LMP, *n* = 123 • Exposure in the first trimester, *n* = 318 • Exposure after first trimester, *n* = 19 • Exposure during entire pregnancy, *n* = 1 • Exposure timing unknown, *n* = 76	As of February 2017: • Known outcomes *n* = 717 (725 infants): ◦ Live births without congenital malformations ▪ Full-term, *n* = 421 ▪ Preterm, *n* = 40 ▪ Neonatal death, *n* = 5 ◦ Live births with congenital malformations ▪ Full-term, *n* = 23 ▪ Preterm, *n* = 5 ▪ Neonatal death, *n* = 0 ◦ Ectopic pregnancies, *n* = 4 ◦ Miscarriages, *n* = 98 ◦ Elective termination, *n* = 126 ◦ Stillbirth, *n* = 3 • Lost to follow-up, *n* = 301 • Outcome pending/unknown, *n* = 229
Ponesimod	Phase 2/3 clinical trial data [134]	20 fetal exposures, all first trimester	• Known outcomes, *n* = 18: ◦ Live births (normal newborn), *n* = 6 ◦ Induced abortion, *n* = 8 ▪ No fetal toxicity, *n* = 5 ▪ Benign hydatidiform mole, *n* = 1 ▪ Unknown, *n* = 2 ◦ Spontaneous abortion, *n* = 4
Ozanimod	Clinical development programme [135]	47 (48 birth results for PwMS)	• Known outcomes: ◦ Live birth without congenital anomaly, *n* = 24 ◦ Live birth with congenital anomaly, *n* = 1 ◦ Premature live birth, *n* = 3 ◦ Ongoing, *n* = 2 ◦ Spontaneous early loss, *n* = 7 ◦ Elective termination, *n* = 9 • Unknown, *n* = 2
Dimethyl fumarate	Prospective, international registry [104]	345 (351 births)	• Known outcomes, *n* = 296: ◦ Live births, *n* = 277 ◦ Loss of fetus, *n* = 19 ▪ Elective/therapeutic termination, *n* = 0 ▪ Spontaneous abortion, *n* = 17 • Ectopic pregnancy, *n* = 1 • Molar pregnancy, *n* = 1 ▪ Stillbirth, *n* = 1 ▪ Unknown, *n* = 1 • Confirmed birth defects, *n* = 8
Cladribine tablets	Worldwide surveillance programme [136]	Maternal cohort: • 180 (all patients exposed to cladribine tablets): 53.9% exposed before pregnancy, 26.3% during first trimester, and 18.4% with unknown timing Paternal cohort: • 22 (all patients exposed to cladribine tablets): 66.7% exposed before pregnancy and 33.3% with unknown timing	Maternal cohort: • Known outcomes, *n* = 76 ◦ Live births, 48.7% ◦ Spontaneous abortions, 21.1% ◦ Ectopic pregnancies, 1.3% ◦ Elective termination, 28.9% Paternal cohort: • Known outcomes, *n* = 9 ◦ Live births, 88.9% ◦ Spontaneous abortions, 11.1% • No cases of ectopic pregnancy or elective termination No cases of major congenital anomalies or stillbirth reported in any cohort

(*Continued*)

Table 3. Continued.

DMT	Source of information	Number of pregnancies (N)	Outcomes
Infusion			
Alemtuzumab	Clinical development programme [137]	264 pregnancies in 160 alemtuzumab-treated women (mean time from last alemtuzumab dose to conception, 35.9 months) 16 conceptions occurred within 4 months, and five within 1 month of the last alemtuzumab dose	• Known outcomes, $n = 233$ (completed): ◦ Live births, $n = 155$ (no congenital abnormalities or birth defects) ◦ Spontaneous abortions, $n = 52$ ◦ Elective abortions, $n = 25$ ◦ Stillbirth, $n = 1$ • Ongoing, $n = 11$ • Unknown, $n = 20$
Ocrelizumab	Clinical development programme and post-marketing sources [118]	3,253 maternal-exposure pregnancies in patients treated with ocrelizumab for MS 2,446 were prospective in nature (i.e. final outcomes were unknown at initial notification)	As of July 2023, of the 1,145 cases with known outcomes: • Live births, $n = 957$ (83.6%) ◦ 61.4% of pregnancies were full term ◦ 8.5% were pre-term ◦ 30.2% had an unknown gestational week • Spontaneous abortions, $n = 95$ • Stillbirth, $n = 1$ • Confirmed major congenital abnormalities, $n = 14$ (one live birth reported two)

Ongoing large post-authorisation safety studies are being conducted for ocrelizumab, cladribine tablets, and ofatumumab.
Within each category, the DMTs are colour-coded for efficacy according to how effectively they reduce the MS relapse rate based on broad categories recommended in guidelines published by the Association of British Neurologists (yellow = moderately effective; grey = more effective than yellow; orange = highly effective) [14].
There are no or limited amount of data on the effect of Siponimod and ublituximab in pregnancy [100, 112, 113, 138].
DMT, disease-modifying therapy; LMP, last menstrual period; MS, multiple sclerosis; PRIM, Pregnancy outcomes Intensive Monitoring; PwMS, people with multiple sclerosis.

counselling, PwMS and their partners might not use the most suitable contraceptive methods, increasing the risk of unintended pregnancies or potentially worsening MS symptoms. Also, the lack of standardised counselling can lead to inconsistent advice from HCPs, causing confusion and gaps in care. Including family planning counselling in MS clinical guidelines and standard care protocols is crucial to address this gap. Additionally, education and training programmes for neurologists, OB-GYNs, nurses, and other RHCPs are needed to ensure they can offer appropriate guidance. Developing patient-centred resources and decision aids will further facilitate informed discussions, considering the patient's disease status, treatment options, and reproductive goals. OB-GYNs are key members of the multidisciplinary team caring for PwMS, particularly for women of childbearing potential receiving DMTs. Close collaboration among OB-GYNs, other RHCPs, and neurologists is important when providing reproductive care for PwMS. Importantly, PwMS and their partners should receive dedicated, tailored counselling to help them make informed decisions around family planning and contraception. Contraceptive decision-making should consider many patient-related factors, as these may influence their suitability for specific contraceptive options. In addition, OB-GYNs and other RHCPs should educate themselves on MS medications, recommendations for use during pregnancy, and any necessary washout periods, so this can be factored into reproductive life planning decisions and discussions in collaboration with other members of the multidisciplinary team.

Conclusions

The detailed information on DMTs provided here should support more comprehensive reproductive life planning counselling and a greater awareness among all stakeholders. This is particularly important because there are gaps in contraception counselling for PwMS, with family planning advice varying depending on the country. Without proper guidance, PwMS and their partners may not use the most suitable contraceptive methods, increasing the risk of unintended pregnancies or exacerbating MS symptoms. Surveys and observational studies should assess current counselling practices by neurologists, OB-GYNs, and primary care providers to identify barriers and standardise care. Research is also needed to understand how MS medications affect hormonal contraceptives and the impact of DMTs on spermatogenesis. Developing and testing educational interventions and decision aids can further support informed contraceptive choices, improving knowledge, satisfaction, and adherence among PwMS. Such studies can lead to evidence-based guidelines that support personalised contraceptive counselling and improve reproductive health outcomes for PwMS.

Note

1. Data are lacking on this topic for gender-diverse individuals, so we are focusing this review on cisgender women, herein described as women.

Author roles

R.E.N. is the corresponding author. All authors contributed to the conception and drafting of the manuscript, from data interpretation to revision of the article for important intellectual content. They also provided final approval for the publication and agreed to be accountable for all aspects of the work, ensuring that any concerns related to the integrity or accuracy of any part of the work were appropriately investigated and resolved.

Ethics statement

This review article does not involve research conducted on human subjects, and therefore, ethical approval was not required.

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Data availability statement

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