



Review

Recommendations for the Treatment of Multiple Sclerosis in Family Planning, Pregnancy and Lactation in Switzerland: Immunotherapy

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Abstract: A large number of disease-modifying immunotherapies are available for the treatment of people with multiple sclerosis. Many disease-modifying immunotherapies show scarce or no safety data in pregnancy and breastfeeding and are labeled as being contraindicated during these periods in the Swiss summary of product characteristics. Some disease-modifying immunotherapies also have restrictions for male patients. Hence, family planning should always be considered in treatment decisions. If clinically necessary, the continuation of immunotherapy during pregnancy can be considered for some substances. In these situations, the “Good Off-Label Use Practice”, careful consideration of the benefit–risk profile, and interprofessional cooperation between the

treating neurologist, obstetrician–gynecologist, and pharmacist/pharmacologist, ideally with the involvement of experienced centers, is necessary. Here, we present an update on disease-modifying immunotherapies in multiple sclerosis with a focus on family planning, pregnancy, and breastfeeding and provide consensus recommendations of the Medico-Scientific Advisory Board of the Swiss Multiple Sclerosis Society, the Swiss Neurological Society, and the Swiss Society for Gynecology and Obstetrics (represented by the Academy of Fetomaternal Medicine). These unified national recommendations are necessary, as guidelines from other countries differ and because of separate approval/reimbursement situations in Switzerland.

Keywords: multiple sclerosis; family planning; immunotherapy and family planning; immunotherapy and pregnancy; immunotherapy and breastfeeding; multiple sclerosis and pregnancy; multiple sclerosis and breastfeeding; multiple sclerosis and family planning

1. Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS) with a prevalence of approximately 174–187/100,000 inhabitants and an estimated 18,000 pwMS (people with multiple sclerosis) in Switzerland [1]. The disease usually manifests in the second to third decade of life and shows a female predominance of 2.3–3.5:1 in young adults [2]. In particular, relapsing forms of MS have seen a significant expansion of disease-modifying therapies (DMTs) [3]. Given the high MS prevalence in women of childbearing age, counseling about family planning is essential. Until the 1990s, women with MS were discouraged from considering pregnancy [4]. However, over the last three decades, it has become clear that pregnancy is not associated with worse MS disease outcomes [5,6]. As specific DMTs risk profiles have emerged, individual benefit–risk assessment also needs to consider family planning.

In Switzerland, neurologists often follow therapeutic guidelines from neighboring countries within the European Medicines Agency (EMA) region. However, significant differences in approvals between Swissmedic and EMA considerably influence the choice of potential DMTs, particularly for women of childbearing age [3]. For a more in-depth description of the discrepancies, we refer to our Swiss treatment commentary [3]. Additionally, discrepancies in safety requirements and monitoring between Switzerland and the EMA lead to variations in DMT usage in clinical practice and monitoring recommendations pre- and postpartum. Also, specific differences, such as wash-out periods before conceiving, argue for a unified national approach to family planning, pregnancy, and lactation to ensure consistent and effective patient care. The interdisciplinary author group (neurologists, pharmacologists/pharmacists, gynecologists/obstetricians) mandated by the Swiss Multiple Sclerosis Society, the Swiss Neurological Society, and the Swiss Society for Gynecology and Obstetrics here provide recommendations for DMTs in the context of family planning, pregnancy, and lactation.

2. Methods

The methodology is in line with the Swiss commentary on immunotherapy in MS first published in 2019 and updated in 2022 [3,7]. Relevant literature was retrieved from PubMed (www.ncbi.nlm.nih.gov (accessed on 24 June 2022)) using the terms “multiple sclerosis” + the specified immunotherapy + “pregnancy” OR “lactation” OR “breastfeeding”. Of the identified articles, only English articles were included. References of selected papers were screened for additional studies which had not been identified before. In addition, the databases “LactMed” (www.ncbi.nlm.nih.gov/books/NBK501922 (accessed on 1 July 2022)), “embryotox” (www.embryotox.de, (accessed on 15 December 2022)), “CRAT” (www.lecrat.fr (accessed on 10 March 2023)), “BUMPS” (www.medicinesinpregnancy.org (accessed on 10 March 2023)), as well as “Brigg’s Drugs in Pregnancy and Lactation Edition 2021” [8] and “Hale’s medications and Mothers’ milk app” (version 6.36.5651) were re-

viewed. Subsequently, all pharmaceutical companies with approved MS immunotherapies in Switzerland were contacted for available post-marketing data.

After the manuscript was drafted by a core group of authors, it was reviewed by the Swiss MS Society (SMSS; multiplesklerose.ch), the Swiss Neurological Society (SNS; swissneuro.ch), and the Swiss Society for Gynecology and Obstetrics (sggg.ch; represented by the Academy of Fetomaternal Medicine). Therefore, this structured commentary corresponds to a consensus within these groups. However, formal criteria were not employed (e.g., DELPHI method), and hence, this structured commentary does not follow formal requirements of a guideline process.

We only discuss disease-modifying drugs that are approved in Switzerland for relapsing multiple sclerosis (RMS) but not symptomatic therapies or secondary progressive multiple sclerosis. Immunotherapies not approved for MS in Switzerland (e.g., rituximab) and treatments for neuromyelitis optica are also not discussed. Recommendations in that regard can, e.g., be extracted from the French MS society [9]. As we only highlight selected aspects related to family planning/pregnancy/lactation for a more comprehensive outline of safety aspects, we refer to the respective CH SmPC (Swiss summary of product characteristics in Appendix A). The discussed recommendations apply to the original preparations as well as to generics.

Some of the recommendations are formally off-label. Therefore, specific safeguards and compliance standards must be observed (see separate paragraph).

3. General Aspects of Immunotherapy and Family Planning

3.1. *Prepartum Management of Immunotherapy*

We recommend discussing family planning already at the time of diagnosis, especially when discussing immunotherapy. The importance of (interdisciplinary) preconception counseling and possibly treatment modification must be highlighted. Both the woman with MS and her partner must be advised about the risk profile of respective DMT use during the conception period and during pregnancy but also during breastfeeding. Early pregnancy needs to be excluded before starting any immunotherapy. Immunotherapies with insufficient safety information in pregnancy or with suspected teratogenic effects should, in general, be avoided in pwMS of childbearing age who are not using an effective contraception method (see below) [10–13]. Substances associated with rebound risk should also be used with caution due to the possible discontinuation before conception (for details, see individual substances and Table 1) [14–20].

When initiating immunotherapy, the choice of the individual DMT, in addition to other factors, depends on disease activity (Table 1) [3]. It is essential to note that “highly active disease” is not uniformly defined and, thus, based on an individualized assessment with an individual judgment call of the treating neurologist [3,7,21]. The individual MS risk profile, assessed on the basis of clinical, radiological, and biological parameters (e.g., relapse rate, new T2 or enhancing lesions on brain MRI, anatomical localization of the lesions), should guide the choice of a DMT [22]. As all DMTs are prophylactic, treatment during the early stages of disease is generally recommended [23]. In addition, intermediate and high-efficacy treatments are now increasingly used early in the disease course, given the impact on long-term prognosis [22]. Particularly in active disease, it is advised not to postpone the initiation of DMTs, regardless of any family planning. In addition, it is recommended that before conception, disease activity is well controlled with a 1-year relapse-free period prior to conception in active MS or even 2 years in highly active MS [6]. This recommendation also includes pwMS already under DMTs. In this situation, the decision to discontinue immunotherapy needs to take into account pre-therapeutic disease activity, risk of disease reactivation, and characteristics of the specific substance (e.g., wash-out interval, risk of rebound activity; Table 2). The wash-out interval should be kept as short as possible, which implies discussions on fertility as well as female and male sexual health. In men, MS-associated symptoms can impact male sexuality and should be addressed.

Table 1. Consensus on disease-modifying therapy options pre- and postpartum in female MS patients of childbearing age. Categorization of disease activity is based on disease activity at start of disease-modifying therapy (baseline). *

Non-Active Relapsing-Remitting MS at Baseline			
Initiation of Treatment with Wish to Conceive in Short to Medium Term	Wash-Out Period before Conception	Treatment Continuation during Pregnancy	Treatment Restart after Delivery
Glatiramer acetate Interferon beta preparations Dimethyl fumarate/diroximel fumarate	Glatiramer acetate/Interferon beta preparations/dimethyl fumarate/diroximel fumarate: stop at pregnancy diagnosis (no washout period) Teriflunomide: accelerated elimination procedure with repeated measurement of drug blood levels before pregnancy planning ‡	Not recommended in non-active RRMS at baseline with stability one year before conception. However, theoretically possible for glatiramer acetate/interferon beta preparations/dimethyl fumarate/diroximel fumarate	If stable during pregnancy, patient can breastfeed. If breastfeeding is not an option, restart previous DMT If disease activity during pregnancy, evaluate DMTs mentioned under “active/highly MS”
Active multiple sclerosis at baseline			
Initiation of treatment with wish to conceive in short- to medium-term	Wash-out period before conception	Treatment continuation during pregnancy	Treatment restart after delivery
Glatiramer acetate Interferon beta preparations Dimethyl fumarate/diroximel fumarate Cladribine (pulsed treatment): complete 2 cycles of treatment before pregnancy planning and follow wash-out period. Natalizumab if anti JCV negative; ocrelizumab if anti JCV positive; ofatumumab if anti JCV positive, and natalizumab/ocrelizumab no feasible alternative	Dimethyl fumarate/diroximel fumarate: stop at pregnancy diagnosis Sphingosine-1-phosphate receptor modulators: consider risk of rebound upon stopping and bridging to other DMT before pregnancy ‡ Wash out period: Fingolimod: 2 months; Ozanimod: 3 months; Ponesimod: 7 days Teriflunomide: accelerated elimination procedure with repeated measurement of blood levels ‡ Cladribine: 6 months wash-out period after the last dose Natalizumab: No wash-out period. Consider risk of rebound upon stopping and bridging to other DMT before pregnancy ‡ or continuation during pregnancy † Ocrelizumab: wash out 2 months before pregnancy planning † Ofatumumab: 80–112 days when planning pregnancy †	Natalizumab: discuss continuation during pregnancy (increased interval dosing to 6–8 weeks with last dose 30–34th gestational week) † Ocrelizumab/ofatumumab possible if clinical situation requires (e.g., relapses during pregnancy), usually not needed	Glatiramer acetate/Interferon beta preparations: breastfeeding possible Dimethyl fumarate/diroximel fumarate: possible as 2nd line during breastfeeding, depending on disease activity during pregnancy † Natalizumab/Ocrelizumab: breastfeeding possible † Ofatumumab: breastfeeding is possible if OCR and NTZ are not a suitable option Sphingosine-1-phosphate receptor modulators/teriflunomide are not recommended while breastfeeding Cladribine is usually not necessary (pulsed treatment)

Table 1. *Cont.*

Highly active multiple sclerosis at baseline			
Initiation of treatment with wish to conceive in short- to medium-term	Wash-out period before conception	Treatment continuation during pregnancy	Treatment restart after delivery
Cladribine (pulsed treatment): completes 2 cycles of treatment before pregnancy planning and follows wash-out period.	Cladribine (pulsed treatment): complete the 2 treatment cycles over 2 years before pregnancy planning and follow 6-month wash-out period after the last dose	No for cladribine (complete pulsed treatment before pregnancy)	Cladribine is usually not necessary (pulsed treatment)
Natalizumab if anti JCV negative; ocrelizumab if anti JCV positive; ofatumumab if anti JCV positive, and natalizumab/ocrelizumab no feasible alternative	Natalizumab: continue during pregnancy † (increased interval dosing to 6–8 weeks with last dose 30–34th gestational week) ‡ Ocrelizumab: wash out 2 months before pregnancy planning †. If disease is stable before pregnancy, it can be stopped during pregnancy (no rebound relapses)	Natalizumab: continue during pregnancy † (increased interval dosing to 6–8 weeks with last dose 30–34th gestational week) ‡ Ocrelizumab is usually discontinued during pregnancy (no rebound relapse); if disease is very active, can be continued during pregnancy †, last dose at 28–30th gestational week	Natalizumab: rapid restart after delivery. Breastfeeding possible † Ocrelizumab: rapid restart after delivery. Breastfeeding is possible, but wait 4 h between pre-infusion antihistamines before next breastfeeding †
Alemtuzumab (pulsed treatment) completes 2 cycles of treatment before pregnancy planning and follows wash-out period.	Ofatumumab until pregnancy diagnosis possible (try synchronization of injection schedules with menses) † Alemtuzumab (pulsed treatment) completes 2 treatment cycles over 2 years before pregnancy planning. Last dose 4 months before conception. Test for thyroid function monthly during pregnancy	Ofatumumab is usually discontinued during pregnancy (no rebound relapse), but if disease is very active, can be continued during pregnancy if OCR and NTZ are not suitable options No for alemtuzumab (complete pulsed treatment before pregnancy). Test for thyroid function monthly during pregnancy	Ofatumumab: rapid restart after delivery if ocrelizumab and natalizumab are not a suitable option Alemtuzumab is usually not necessary (pulsed treatment). Not a treatment option while breastfeeding

Abbreviations: relapsing–remitting multiple sclerosis (RRMS), disease-modifying therapy (DMT), persons with multiple sclerosis (pwMS). John Cunningham virus (JCV). * As signs of activity relapses and new T2/FLAIR or gadolinium-enhancing lesions (MRI) are commonly used. Especially for the term “highly active”, no general definition exists; it is, therefore, a judgment call, which is subject to the appropriate assessment of the individual case and is in the competence of the treating physician, see also Friedli et al [3]. † Constitutes off label recommendation. ‡ For further details, we refer to the relevant chapter on specific immunotherapies in this manuscript.

Table 2. Overview of disease-modifying therapies and their use in pregnancy/breastfeeding.

DMT	Pharmacokinetics	Preclinical Data for Pregnancy	Evidence for Exposure during Pregnancy	Exposure during Breastfeeding	Reproductive Data in Men	CH SmPC	Our Recommendations
Interferon beta preparations	$t_{1/2}$: 5–78 h PT: unknown but unlikely (high molecular weight) [26]	Dose-dependent abortive effect from 3-fold the human dose [26–29]	No evidence for increased risk for spontaneous abortions or major malformations in >3500 pregnancies [30–44]	RID < 0.1% Breastfed infant exposure unlikely due to poor oral bioavailability [45–47] No adverse events in 40 exposed infants [45,48–51]	No data on fertility available, but an effect on spermatozoid genetic material not expected [26] Few clinical cases with no evidence of embryo–fetal toxicity [52–54]	Pregnancy: may be used when clinically necessary Breastfeeding: can be used Contraception: n/a	The safety profile in pregnancy makes it a first-choice drug in pregnant pwMS if IFNB was the appropriate treatment beforehand (RRMS with no/low disease activity). We generally consider IFNB safe in breastfeeding and to be one of the preferred DMTs for treating MS during breastfeeding when effective. In men, IFNB can be used without restriction.
Glatiramer acetate	$t_{1/2}$: unclear PT: unlikely as parent drug degraded at injection site [55]	None [55].	No evidence of increased risk for spontaneous abortions or major malformations in >5500 pregnancies [34,49,56–60].	RID 0.2% data [55] Breastfed infant exposure unlikely due to poor oral bioavailability [8]. No adverse events in more than 100 exposed infants [49,51,58,61,62]	No data on fertility available, but an effect on spermatozoid genetic material not expected Few clinical cases with no evidence for embryo–fetal toxicity [52–55].	Pregnancy: may be used when clinically necessary Breastfeeding: can be used Contraception: n/a	The safety profile in pregnancy makes it a first-choice drug in pregnant pwMS if GA was the appropriate treatment beforehand (RRMS with low disease activity). We generally consider GA as safe in breastfeeding and to be one of the preferred DMT during breastfeeding. In men, GA can be used without restriction.
Teriflunomide	$t_{1/2}$: 18–19 d PT: yes [13]	Growth disturbance, malformations, embryo–fetal death in even small doses [13] At supratherapeutic doses reduction in sperm count and semen DNA alteration [63].	In nearly 400 patients, pregnancy outcomes were comparable to general population [64–66] No teratogenic effects in >1000 leftunomide-exposed pregnancies [67,68]	RID unknown Proven in animal data [13] No clinical data available [13] Accumulation in infant possible due to long $t_{1/2}$	Transition in human semen, with possible transmission to partner during intercourse [69,70] No mutagenic/clastogenic effects in preclinical tests, and few clinical cases published [69]	Pregnancy: must not be used Breastfeeding: must not breastfeed during treatment Contraception: contraindicated without reliable contraception; must be continued after discontinuation and rapid elimination until plasma levels < 0.02 mg/L	Not a treatment option during pregnancy because of the teratogenic effects observed in preclinical models and the availability of safer alternatives. TERI is not a treatment option during breastfeeding. In men, TERI can be used without restriction.
Dimethyl fumarate	$t_{1/2}$: 1 h PT: likely due to low molecular weight [71]	Lower birth weight, ossification disorders, maternal toxicity at 3 times the human dose, increased miscarriage rate at 16 times the human dose [72]	>500 first-trimester exposures published with pregnancy outcomes comparable to general population [72–77].	RID < 0.02% [78] No clinical data available [72]	No mutagenic/clastogenic effects in preclinical tests No clinical data available [72]	Pregnancy: should only be used if the benefits outweigh the risks Breastfeeding: must not breastfeed during treatment Contraception: n/a	The safety profile in pregnancy makes it a possible choice in pregnant pwMS if DMF/DRF was the appropriate treatment beforehand + (active RRMS, continuation of treatment). DMF/DRF can be evaluated as treatment during breastfeeding because the very low RID suggests limited exposure of the infant +. In men, DMF/DRF can be used without restriction.
Diroximel fumarate	$t_{1/2}$: 1 h PT: see dimethyl fumarate	Lower birth weight, skeletal abnormalities, increase in embryofetal deaths at supratherapeutic doses [79].	No clinical data specific to diroximel fumarate	Probably same RID as Dimethyl fumarate [80] No clinical data specific to diroximel fumarate [80]	No mutagenic/clastogenic effects in preclinical tests No clinical data available [79]	Pregnancy: should only be used if the benefits outweigh the risks Breastfeeding: must not breastfeed during treatment	The safety profile in pregnancy makes it a possible choice in pregnant pwMS if DMF/DRF was the appropriate treatment beforehand + (active RRMS, continuation of treatment). DRF can be evaluated as treatment during breastfeeding because the very low RID suggests limited exposure of the infant +. In men, DMF/DRF can be used without restriction.

Table 2. Cont.

DMT	Pharmacokinetics	Preclinical Data for Pregnancy	Evidence for Exposure during Pregnancy	Exposure during Breastfeeding	Reproductive Data in Men	CH SmPC	Our Recommendations
Fingolimod	t _{1/2} : 6–9 d PT: yes [81]	At doses below human dose, increased incidence of malformations and embryo–fetal mortality (most commonly persistent truncus arteriosus and ventricular septal defects) [10,82]	>1000 first trimester exposure published with pregnancy outcomes comparable to general population [83,84] As reported by EMA, there is a 2-fold increased risk of birth defects on basis of EUROCAT data [85]	No clinical data available Accumulation in infant possible due to long t _{1/2} RID unknown but transfer likely	Low doses detected in male semen, and potentially very low, clinically not relevant plasma concentrations in the sexual partner [86] No mutagenic/clastogenic effects in preclinical tests [10]	Pregnancy: must not be used Breastfeeding: must not breastfeed during treatment Contraception: effective contraception necessary until 2 months after discontinuation	S1PRMs are not a treatment option in pregnancy because of the teratogenic effects observed in preclinical models, the availability of safer alternatives, and the possible teratogenic signal observed in humans. Due to the lack of data, S1PRMs are not a treatment option during breastfeeding. In men, S1PRMs can be used without restriction.
Ozanimod	t _{1/2} : 10 d PT: probably similar to Fingolimod	embryo–fetal death, abnormal and delayed ossification, visceral anomalies and malformations of the large blood vessels [87]	<100 clinical cases without evidence for increased risk of adverse pregnancy outcomes [88]	Proven in animal data [87] RID unknown No clinical data available Accumulation in infant possible due to long t _{1/2}	No mutagenic/clastogenic effects in preclinical tests [87].	Pregnancy: must not be used Breastfeeding: must not breastfeed during treatment Contraception: effective contraception necessary until 3 months after discontinuation	S1PRMs are not a treatment option in pregnancy because of the teratogenic effects observed in preclinical models, the availability of safer alternatives, and the possible teratogenic signal observed in humans. Due to the lack of data, S1PRMs are not a treatment option during breastfeeding. In men, S1PRMs can be used without restriction.
Ponesimod	t _{1/2} : 33 h PT: probably similar to Fingolimod	embryo–fetal death, severe disturbances in morphological development and embryo–fetal growth, teratogenic effects [89]	Few clinical cases without evidence of increased risk of adverse pregnancy outcomes [90,91]	Proven in animal data with decreased survival rate, body weight gain, and delayed sexual maturation in offspring [89] No clinical data available Accumulation in infant possible due to long t _{1/2}	No mutagenic/clastogenic effects in preclinical tests [89]	Pregnancy: must not be used Breastfeeding: must not breastfeed during treatment Contraception: effective contraception necessary until 1 week after discontinuation	S1PRMs are not a treatment option in pregnancy because of the teratogenic effects observed in preclinical models, the availability of safer alternatives, and the possible teratogenic signal observed in humans. Due to the lack of data, S1PRMs are not a treatment option during breastfeeding. In men, S1PRMs can be used without restriction.
Cladribine	t _{1/2} : 7–19 h PT: likely (low molecular weight) [92,93].	Increased risk for severe malformations and embryonic death rate [11]	Less than 70 cases published without major clinical concerns so far [94–96]	RID 3% [97,98] Undetectable after 48 h in one patient [99] No clinical data available	Testicular changes in preclinical tests [11]. Due to mutagenicity of cladribine, genetic changes in sperm cells possible [12].	Pregnancy: must not be used Breastfeeding: contraindicated until 1 week after last dose Contraception: effective contraception necessary up to 6 months after last dose	CLAD is not a treatment option in pregnancy because of the teratogenic effects observed in the preclinical models and the absence of human safety data in pregnancy. Breastfeeding should be withheld for one week after the last dose of cladribine. In both women and men, contraception should be used for six months after the last CLAD dose.

Table 2. Cont.

DMT	Pharmacokinetics	Preclinical Data for Pregnancy	Evidence for Exposure during Pregnancy	Exposure during Breastfeeding	Reproductive Data in Men	CH SmPC	Our Recommendations
Natalizumab	t _{1/2} : 16 d PT: expected from 14 GW as for endogenous IgG4-antibody	Abortive effect at 7-fold, hematological abnormalities and morphological changes at 2.4-fold the human dose [100]	>1000 cases first trimester exposures without major warning signals [101–105]; recent data with probable higher risk for small gestational age [106] Up to 61% of neonates of mothers treated up to the third trimester with transient anemia, thrombocytopenia, and reversible leukocytosis have been reported [102,106–108]	RID 0.22%, very low concentration measured [109–111] Breastfed Infant exposure unlikely due to poor bioavailability (i.e., polypeptide structure, probably destroyed in the gastrointestinal tract) Approx. 40 infants without adverse events [111,112]	No disruption of the hormonal axis or fertility in 7 men [113].	Pregnancy: should not be used unless clinical findings necessitate treatment Breastfeeding: should be discontinued during treatment Contraception: n/a	NTZ safety profile in pregnancy makes it a first-choice drug in pwMS during pregnancy when NTZ was the appropriate treatment beforehand †. NTZ can also be used if the clinical situation requires intensification of previous immunotherapy during pregnancy. NTZ can be evaluated as second-line treatment during breastfeeding because the very low RID and poor oral bioavailability suggest limited exposure of the infant†. In men, NTZ can be used without restriction.
Ocrelizumab	t _{1/2} : 26 d PT: expected from 14 GW as for endogenous IgG1-antibody	Transient B-cell depletion of the offspring with repopulation starting after 6 months [114].	Pregnancy outcomes comparable to the general population in ~500 first-trimester exposures [115–119] Possible neonatal hematological toxicity with transient lymphopenia [115] Possible increased risk of maternal–fetal infections [115].	RID < 1% [118] Breastfed Infant exposure unlikely due to poor bioavailability (i.e., polypeptide structure, probably destroyed in the gastrointestinal tract) >60 infants exposed through breast milk without reported adverse events [111,119]	No disruption of the hormonal axis or fertility in nine men [113]	Pregnancy: should not be used unless clinical findings necessitate treatment Breastfeeding: should be discontinued during treatment Contraception: use reliable contraception during and up to 6 months after last infusion	OCR safety profile in pregnancy makes it a 2nd-choice drug in pregnant pwMS when OCR was the appropriate treatment beforehand †. In this patient population, OCR can be evaluated as second-line treatment during breastfeeding because the very low RID and poor oral bioavailability suggest limited exposure of the infant†. In men, OCR can be used without restriction.
Ofatumumab	t _{1/2} : 16 d PT: expected from 14 GW as for endogenous IgG1-antibody	B-cell depletion of the fetus, reduction of the humoral immune response, and decrease in spleen weight at 160 times the human dose [120]	30 exposed pregnancies reported without adverse outcomes reported [121].	RID 0.03% Breastfed Infant exposure unlikely due to poor bioavailability (i.e., polypeptide structure, probably destroyed in the gastrointestinal tract [122] 12 infants exposed with no B-cell depletion in available B-cell measurements (n = 5) [122]	No clinical data available No mutagenic/clastogenic effects in preclinical tests [120]	Pregnancy: should not be used unless clinical findings necessitate treatment Breastfeeding: benefits of breastfeeding should be considered along with the benefits of treatment Contraception: use reliable contraception during and up to 6 months after last infusion	OFA should only be used during pregnancy and breastfeeding if the clinical need is appropriate and alternatives with more data (natalizumab, ocrelizumab) are not feasible. In men, OFA can be used without restriction.

Table 2. *Cont.*

DMT	Pharmacokinetics	Preclinical Data for Pregnancy	Evidence for Exposure during Pregnancy	Exposure during Breastfeeding	Reproductive Data in Men	CH SmPC	Our Recommendations
Alemtuzumab	t _{1/2} : 4–5 d PT: expected from 14 GW as for endogenous IgG1-antibody	At 2.4 times the human dose increased embryo–fetal mortality, there is reduced number of corpora lutea and implantation sites [12]	271 exposed pregnancies without major warning signals [123–125].	Proven in animal data [12] RID unknown Breastfed Infant exposure unlikely due to poor bioavailability (i.e., polypeptide structure, probably destroyed in the gastrointestinal tract) No clinical data	Higher proportion of abnormal spermatozoa in preclinical tests [12] No clinical data available	Pregnancy: should not be used unless clearly necessary Breastfeeding: should be discontinued until 4 months after the last infusion Contraception: use reliable contraception during and up to 4 months after last infusion	ALE is considered a third-line treatment. Due to the absence of data in pregnancy and possible neonatal hematological toxicity, ALE should not be used during pregnancy unless in situations with no other therapeutic option. We do not consider ALE a suitable immunotherapy during breastfeeding. In men, ALE can be used without restriction.

Abbreviations: DMT: disease-modifying treatment, CH SmPC: Swiss summary of product characteristics, P: pregnancy, BF: breastfeeding, t_{1/2}: half-life, h: hours PT: placental transfer, RID: relative infant dose, P: pregnancy, BF: breastfeeding, n/a: not specified, GW: gestational week, d: days, EUROCAT: European network of population-based registries for the epidemiological surveillance of congenital anomalies, (CH SmPC): Swiss summary of product characteristics, GA: glatiramer acetate, IFNB: interferon beta preparations, DMF: dimethyl fumarate, DF: diroximel fumarate, TERI: teriflunomide, CLAD: cladribine, S1PRM: sphingosin-1-phosphate receptor modulators, NTZ: natalizumab, OCR: ocrelizumab, OFA: ofatumumab, ALE: alemtuzumab; †: off-label recommendation.

In pwMS with a highly active disease course and a higher risk of disease activity, the continuation of selected immunotherapies during pregnancy can be considered, which requires a careful benefit–risk assessment, ideally in cooperation with a specialized MS center in multi-disciplinary cooperation (e.g., obstetrician–gynecologist, pharmacist, advanced practice midwife, neonatologists). In the aforementioned discussion with the pwMS, it is crucial to transparently present both benefits and risks, enabling informed consent for the treatment.

Counseling about Contraception

At the initiation of treatment and in the absence of a desire for pregnancy, contraception must be introduced in cooperation with an obstetrician–gynecologist. Under certain immunotherapies, the use of a safe and effective contraception method must be recommended (teriflunomide, S1PRMs (sphingosin-1-phosphate receptor modulators), cladribine, ocrelizumab, ofatumumab, alemtuzumab), especially in view of the high rate of unplanned pregnancies in the general population in high-income countries (up to 50% of all pregnancies) [24]. Different considerations may apply for treatments which have to be taken continuously versus “pulsed” therapies, which are only administered over a few days a year for a few years (see Cladribine, Alemtuzumab). In general, hormonal contraceptives do not affect the clinical disease course and do not interact with currently licensed immunotherapies [25]. Some symptomatic medications (e.g., lamotrigine, carbamazepine, topiramate; not discussed in this paper) may decrease the efficacy of hormonal contraceptives. Cladribine requires six months of contraception in women and also in men. While in the past, a dual contraception (hormonal and barrier method) for four weeks after the last dose of cladribine in women was recommended due to recent data showing a lack of interaction between cladribine and hormonal contraceptives, this recommendation has been revised [11].

If a pregnancy is planned, counseling about appropriate folic acid/vitamin intake before ceasing contraception must not be forgotten, as in all women planning pregnancy. This is even more important if the woman is under antiepileptic treatment, as in this case, a high-dose folic acid intake to prevent neural tube defects is usually indicated.

If an unplanned pregnancy occurs during treatment with a drug with an unknown risk profile for pregnancy or preclinical teratogenic effects and teratogenic signals, the woman should be referred to an obstetrician/feto-maternal medicine specialist. Additionally, a pharmacovigilance center, the Swiss Teratogen Information Service (STIS; www.swisstis.ch, accessed on 9 March 2023), should be contacted to provide an individual risk assessment. It is, however, essential to emphasize that exposure to such treatment with an unknown risk profile or known warning signals in early pregnancy is not, by itself, an indication for the termination of pregnancy.

In men, the impact of immunotherapy on reproduction needs to be accounted for (e.g., direct mutagenic effect, disruption of spermatogenesis, transfer of substances through the semen) [52,126]. For a few agents (e.g., mitoxantrone and cyclophosphamide, both currently only used in exceptional cases), cryopreservation of semen needs to be offered prior to therapy. Special considerations for cladribine are mentioned in the relevant paragraph.

3.2. Postpartum Management of Immunotherapy

Older studies indicate a reduction in the relapse rate, especially in the second and third trimester of pregnancy, with a higher risk of disease reactivation in the postpartum phase [127]. More recent studies point to a lower risk for postpartum disease reactivation; however, the study results are heterogeneous [128–130]. The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months [131–134]. Exclusive breastfeeding probably has a protective effect on postpartum MS disease activity and, therefore, may be considered for pwMS with a mild to moderate disease course with postponed DMT reintroduction [128,130,135]. In highly active disease, a rapid initiation of potent immunotherapy post-partum is necessary. The possibility of breast-feeding will

then depend on the safety profile of DMT in breastfeeding and will be discussed below for each DMT. If the mother decides not to breastfeed, immunotherapy should be restarted as early as possible [131].

3.3. MRI Monitoring of Disease Activity during Pregnancy, Post-Partum, and Lactation

The use of magnetic resonance imaging (MRI) for maternal, placental, or fetal diagnostic purposes is widely documented, mainly at 1.5 Tesla. To date, no harmful fetal or neonatal consequences have been reported [136,137]. Due to the report of a possible rare risk for stillbirth, inflammatory skin disorders, and neonatal death, gadolinium-based contrast agents should only be used if absolutely clinically necessary [138]. During pregnancy, MRI monitoring of disease activity is possible if needed (e.g., for therapeutic consequences such as plasma exchange or suspicion of comorbidities such as cerebral venous thrombosis) [138]. There is no limitation to performing MRIs during the post-partum/lactation period and a new baseline brain MRI 2–3 months postpartum is recommended [138]. New and enlarged T2 lesions indicate disease activity; however, this requires a comparable scan taken before pregnancy in a reproducible fashion [138].

The amount of gadolinium excreted in breast milk is less than 1% of the amount permitted for infants. In addition, gadopentetate has poor oral bioavailability [138]. Thus, it is not expected to be associated with significant systemic exposure in the breastfed infant. Therefore, while in the past, discarding the milk obtained by pumping before breastfeeding was recommended, more recently, this has been abandoned [136,138,139]. If additional safety is desired by the patient, waiting two half-lives (e.g., four hours for gadolinium) can be considered.

3.4. Obstetrical Pre- and Postpartum Follow-Up

Pregnant women with MS have a slightly higher risk for preterm birth and a higher probability for labor induction; most other pregnancy outcomes—such as intrauterine growth restriction—do not differ compared to healthy women [140]. Nevertheless, particularly women with MS and DMT use during pregnancy should be followed more closely due to possible intrauterine growth restriction, preterm birth, placental abruption, intrauterine fetal death, maternal infection, and the limited data availability for most DMTs [141]. In general, the care of pregnant women with MS should be individualized according to the severity of the disease. Early specialized ultrasound of the fetus and close follow-up examination are recommended, especially in women with DMTs, in order to exclude fetal anomalies or early signs of adverse pregnancy outcomes. Major embryonal and fetal organogenesis is confined to the first 12 weeks of gestation; thereafter, mainly, the fetal brain is still subject to differentiation. The mode of delivery primarily depends on obstetric factors. However, neurologic pelvic floor symptoms such as urinary or defecation problems, spasticity as well as the desire of the woman need to be taken into account. A pre-existing neurologic deficit in the legs should be documented by the anesthetist/neurologist before birth, specifically before regional anesthesia. Counseling for the woman by an anesthesiologist before birth might be helpful in cases where there are pre-existing neurologic deficits. If DMT exposure occurs or is planned during pregnancy, the necessity of obstetrical surveillance eventually should be adapted depending on the specific DMT used (for details, see individual substances).

3.5. Drug Safety in Pregnancy and Lactation

Current CH SmPC approvals require different “wash-out” intervals between cessation of DMT and conception. The approvals are generally conservative as the time windows are much longer than the actual time required for DMT elimination. After five half-lives, a drug is ~97% eliminated, and this is commonly considered safe. A more conservative approach would be to wait until after seven half-lives (~100% elimination) [142].

Available safety data during pregnancy and lactation are scarce for most of the approved agents in MS. As pregnancy is a common exclusion criterion in clinical trials, most

information is collected after the drug has been approved (observational cases collections, registry data, and health care databases [143]). Thus, knowledge of reproductive safety relies essentially on retrospective observational data with its methodological caveats and inability to draw valid causal inferences. Additionally, reporting is only mandatory in the case of resulting complications under immunotherapy during pregnancy and breastfeeding. For precise estimates of potential reproductive risks, a large amount of data is required. Thus, for the detection of a 10-fold increased risk of major malformations (calculated on a baseline risk of 3%), prospective data of at least 300 first-trimester exposed pregnancies with known pregnancy outcomes is required, and more than 1000 for the detection of a two-fold increased risk [144]. Therefore, we argue for a cautious interpretation of information derived from smaller datasets, even more so when considering rare but major malformations (e.g., specific cardiac malformations) or other less prevalent pregnancy outcomes. Estimates for rare malformations are unfeasible with data from most current registries and postmarketing surveillance, necessitating reliance on expert opinions and recommendations.

Due to the lack of epidemiological studies on breastfeeding during immunotherapy, common methods for assessing drug safety include estimating the transfer of substances into human milk and evaluating the exposure of the infant. The amount of drug available through human milk is mostly low as it reflects the maternal plasma concentration and not the applied dose. The clinically most relevant parameter to evaluate the level of drug exposure for the infant through breast milk is the Relative Infant Dose (RID). RID is a weight-normalized parameter calculated by dividing the dose of a drug ingested via milk (mg/kg/day) by the mother's dose in mg/kg/day. The level of exposure is also correlated to the volume of ingested milk (full breastfeeding > partial breastfeeding > prelactation state). However, non-dose dependent toxic effects and situations with a risk of accumulation in the infant (e.g., long half-lives and prematurity) also have to be considered [145].

3.6. General Considerations on DMT Use in Pregnancy Outside the Approval (Off-Label Use)

The relative lack of information on drug safety during pregnancy and lactation is reflected in the restrictions for individual DMT regarding pregnancy and breastfeeding in the respective SmPC. In general, many drugs that are prescribed to pregnant or breastfeeding women constitute off-label use. Off-label medicine use implies numerous ethical and legal challenges for healthcare professionals, rendering it a complex and potentially disconcerting practice for those involved. Yet, off-label use is considered essential in areas of unmet medical need and is considered justifiable if the medical need cannot be fulfilled with available licensed medicines or formulations and, in the light of the available evidence, the reasonable chances of efficacy outweighing the likely risks [146]. To guide practice, the principles of Good Off-Label Use Practice (GOLUP) should be respected [146]. Off-label use is defined as the use of a ready-to-use authorized pharmaceutical product deviating from the expert information approved by the competent authorities (SAMS Medical Ethical Guideline). In Switzerland, there is no established administrative practice regarding the new regulation on off-label use. The decision for off-label use rests with the treating physicians, and they are entitled to proceed if the applicable standards are met. A crucial component of the GOLUP guidelines is ensuring that patients receive adequate information about potential risks associated with the prescribed medication for unborn or breastfed infants, which applies especially to therapies with a lack of scientific data [147].

4. Specific Immunotherapy Considerations

We primarily focus on relapsing MS as pregnancy considerations occur infrequently in progressive pwMS. It is essential to outline that, especially in active and highly active MS, the selection of a specific DMTs needs to focus on efficacy and not solely depend on its safety during (potential) pregnancy and lactation. An important goal is to avoid undertreatment with the long-term disability risk of a young mother. It is essential to

discuss with the pwMS the dual considerations of her own risks and those posed to the baby by exposure to disease-modifying therapies.

For detailed information about available preclinical and clinical data in the pre-/postpartum phase, as well as pharmacokinetics and Swiss (CH) guidelines on contraception, we refer to Table 2. Table 1 gives an overview of specific DMT options categorized by disease activity at the start of the disease and different time points in pre-/postpartum care. In men, we highlight detailed recommendations only if available evidence shows potential risks.

4.1. Injectable Therapies

Interferon beta preparations have a large molecular weight, and glatiramer acetate is degraded at the injection site, making placental transfer unlikely, a fact supported by clinical data [26,55]. Consequently, their transfer into breast milk is also impeded, and their RIDs are very low (<0.2%). In addition, these injectables—not intended for oral intake—will be degraded in the infant's gastrointestinal tract and are considered safe while breastfeeding [45–47].

4.1.1. Interferon Beta Preparations (Avonex[®], Betaferon[®], Plegridy[®], Rebif[®])

Interferon beta preparations (IFNB) are considered safe in pregnancy and lactation due to significant data on the first trimester without warning signs [30–44]. However, current data do not allow a risk assessment for rare malformations, and much less information is available for the second and third trimesters.

It is a suitable option for pwMS of childbearing age if the disease is considered non-active at baseline and safety is a major concern of the pwMS.

If pregnancy is planned, IFNB can be continued until the detection of pregnancy without wash-out. Treatment during pregnancy should only be considered for pwMS with a high risk for disease reactivation and pretreatment with an IFNB, which has led to stability.

Breastfeeding is considered safe while treated with IFNB [45,48–51]. However, in non-active MS at baseline without disease activity during pregnancy, there is usually no DMT required in the postpartum period. If the pwMS decides not to breastfeed, an immediate DMT restart is recommended.

Recommendation: The safety profile of IFNB in pregnancy makes it a first-choice drug in pregnant pwMS if IFNB was the appropriate treatment beforehand (RRMS with no/low disease activity) (Table 1). We generally consider IFNB safe in breastfeeding and to be one of the preferred DMTs for treating MS during breastfeeding. In men, IFNB can be used without restriction.

4.1.2. Glatiramer Acetate (Copaxone[®], Glatiramyl[®])

Glatiramer acetate (GA) is considered safe in pregnancy and lactation due to the significant amount of available clinical data regarding the first trimester of pregnancy and the encouraging preclinical data without any warning signs [34,49,56–60]. However, current data do not allow a risk assessment for rare malformations, and much less safety information is available for the second and third trimesters.

It is a suitable option for pwMS of childbearing age if the disease is considered non-active at baseline and safety is a major concern of the pwMS.

If pregnancy is planned, GA can be continued until the detection of pregnancy without wash-out. Treatment during pregnancy should only be considered for pwMS with a high risk for disease reactivation and pretreatment with GA, which has led to stability.

Breastfeeding is considered safe while treated with GA [51,57,58,61,62]. However, in non-active MS at baseline without disease activity during pregnancy, usually there is no DMT required in the postpartum period. If the pwMS decides not to breastfeed, an immediate DMT restart is recommended.

Recommendation: The safety profile the GA in pregnancy makes it a first-choice drug in pregnant pwMS if GA was the appropriate treatment beforehand (RRMS with low

disease activity) (Table 1). We generally consider GA safe in breastfeeding and to be one of the preferred DMTs during breastfeeding. In men, GA can be used without restriction.

4.2. Oral Therapies

Available oral treatments are generally small molecules with low molecular weights, which makes placental passage likely, as demonstrated for some (teriflunomide, sphingosine-1-phosphate receptor modulators) [10,13]. Moreover, all oral treatments except dimethyl fumarate/diroximel fumarate (DMF, DRF) have long half-lives, increasing the likelihood of significant exposure due to accumulation [8]. Corresponding experimental data have shown warning signs for all but DMF/DRF [10,11,13]. In particular, cladribine, due to its mechanism of action, has mutagenic potential and should be avoided during pregnancy; treatment cycles should be completed before attempting to conceive [11]. DMF/DRF has a very short half-life and shows no clear warning signs at doses equivalent to those used in humans, suggesting that it could theoretically be used during pregnancy and breastfeeding [72].

4.2.1. Teriflunomide (Aubagio® , Teriflunomid Sandoz/Spirig HC/-Mepha)

Preclinical data point to a teratogenic effect of Teriflunomide (TERI) [13]. Even though no clear teratogenic effect has, thus far, been observed in human data and the parent drug leflunomide, overall data are limited, and a strict contraindication for pregnancy exists [65–68]. Therefore, TERI is not an option for pwMS when there is a wish to conceive in the short/medium term or with a risk of unplanned pregnancy.

If exposure to TERI occurs during the initial trimester of pregnancy, an early morphological ultrasound should be performed (following preclinical data with a focus on the cephalic pole and skeleton). A TERI-exposed pregnancy should be followed in close collaboration with an obstetrician/feto-maternal medicine specialist and an MS specialist center and reported to the STIS (www.swisstis.ch, accessed on 4 May 2023)).

Because TERI is highly reabsorbed via the enterohepatic circulation, without an active elimination procedure, it takes an average of eight months (up to 24 months) to reach the plasma level of <0.02 mg/L, which is considered safe for conception by the drug manufacturer [13]. Therefore, if a woman receiving TERI therapy plans a pregnancy or if a pregnancy is confirmed during the treatment, it is recommended to use an accelerated elimination procedure with activated charcoal or cholestyramine (e.g., cholestyramine 24 g/day for 11 days), followed by repeated measurements of plasma levels [66].

Due to the lack of data and its risk for accumulation in the breastfed infant, breastfeeding is not advised under treatment with TERI [13,148,149]. If the pwMS decides not to breastfeed, an immediate restart of DMT is recommended.

In male pwMS, TERI has been detected in human semen and can also be transmitted in low, probably clinically irrelevant doses to the female partner during sexual intercourse [70]. Both Swissmedic and the EMA consider the risk of embryo–fetal toxicity to be low and do not recommend discontinuation before a partner’s planned pregnancy [13,149]. In contrast, the Food and Drug Agency (FDA) recommends the termination of therapy, including an accelerated wash-out [150]. In everyday practice, the pwMS should be informed about the available data so that an individual decision can be made.

Recommendation: TERI is not a treatment option during pregnancy because of the teratogenic effects observed in preclinical models. TERI is not a treatment option during breastfeeding. In men, TERI can be used without restriction.

4.2.2. Dimethylfumarate (Tecfidera®)/Diroximel Fumarate (Vumerity®)

The limited clinical data on DMF have found no increased risk for major adverse effects [73–77]. Data for DRF are lacking [79]. Preclinical data show warning signs only at supratherapeutic doses [72].

DMF/DRF can be a treatment option for pwMS with non-active/active MS at baseline. Due to the short half-life (~1 h), DMF/DRF can be continued until the detection of

pregnancy without wash-out. As in non-active/low-active MS at baseline, DMT is usually not needed during pregnancy, and DMF/DRF generally should be discontinued; according to the approval, it could be continued after careful benefit–risk assessment. Continuation of treatment could be an option in MS active at baseline with mild disease activity shortly before pregnancy but should then be managed by an experienced interdisciplinary team.

Treatment during breastfeeding could be evaluated due to the very low RID and lack of warning signs [77,78]. However, clinical data are sparse. In pwMS with disease activity during pregnancy or highly active MS, a highly efficacious DMT should be initiated (Natalizumab or anti-CD20).

Recommendation: The safety profile of DMF/DRF in pregnancy makes them a possible choice in pregnant pwMS if DMF/DRF was the appropriate treatment beforehand (active RRMS, continuation of treatment). DMF/DRF can be continued until the detection of pregnancy without wash-out. DMF/DRF is not recommended during breastfeeding, but the very low RID suggests limited exposure to the infant. In men, DMF/DRF can be used without restriction.

4.2.3. Sphingosine-1-Phosphate Receptor Modulators (Fingolimod/Gilenya[®], Fingolimod Accordis/-Mepha/Sandoz/Devatis/Viatrix; Ozanimod/Zeposia[®]; Ponesimod/Ponvory[®])

Preclinical data point to a teratogenic effect of sphingosine-1-phosphate receptor modulators (S1PRMs) [10,82]. Even though no clear teratogenic effect has, thus far, been observed in human data (Table 2) based on data reported by the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT), an EMA review concluded that fingolimod is associated with a two-fold increased risk of congenital malformations compared with the observed rate in the general population [83–85]. Therefore, it is not a treatment option in pregnancy. In addition, because of the potential of severe rebound activity after discontinuation, S1PRMs are not an optimal option for pwMS with a wish to conceive in the short/medium term or with a risk of unplanned pregnancy.

When exposure to S1PRMs occurs during the initial trimester of pregnancy, an early morphological ultrasound should be performed (following preclinical data with a focus on the cardiovascular system). An S1PRMs-exposed pregnancy should be followed in close collaboration with the obstetrician/feto-maternal medicine specialist, an MS specialist center, and reported to the STIS (www.swisstis.ch (accessed on 4 May 2023)).

If pregnancy is planned in a pwMS treated with S1PRMs, adherence to the different wash-out periods is essential (Table 2). Potentially severe rebound activity (disease activity disproportionate to the activity pattern before treatment) can occur in approximately 10% of cases on average 6–8 weeks after the cessation of fingolimod, which can lead to new long-term disability in 6% of patients [14–16,151]. It is currently not known if a similar rebound risk applies to newer S1PRMs as well. Therefore, close clinical monitoring, if possible, additionally by brain MRI is recommended. There is the possibility of bridging to another immunotherapy before pregnancy to try to avoid rebound activity. Bridging with IFNB/GA is sometimes discussed [152]; the authors do not judge this approach as feasible to safely mitigate the rebound disease risk. Many centers turn to anti-CD20 antibodies or natalizumab (especially in anti JCV-negative patients) to stabilize active disease. However, due to a lack of higher-class evidence, especially on the choice of the respective substance, there is no consensus among the authors.

Due to the lack of clinical/preclinical data for breastfeeding and its risk for accumulation in the breastfed infant, S1PRMs are not a treatment option while breastfeeding. If the pwMS decides not to breastfeed, treatment should be restarted immediately after delivery.

Recommendation: S1PRMs are not a treatment option in pregnancy because of the teratogenic effects observed in preclinical models, the association with a potential rebound effect in case of discontinuation before conception, and the possible teratogenic signal

observed in humans. Due to the lack of data, S1PRMs are not a treatment option during breastfeeding. In men, S1PRMs can be used without restriction.

4.2.4. Cladribine (Mavenclad®)

Preclinical data point to a teratogenic effect of cladribine (CLAD) [11]. Even though no teratogenic effect has, thus far, been observed in human data, it is not a treatment option in pregnancy [94–96]. Therefore, according to the label, contraception has to be applied for the first six months after treatment [11]. However, as this drug is only given during short cycles over two subsequent years with long intervals in between (pulsed treatment), it can be an option for pwMS in childbearing age with active MS, especially with a wish to conceive in the medium/long term (Table 1).

Considering half-life (\approx 4–6 days), the wash-out interval imposed by the label (6 months) is conservative [11]. Nevertheless, we endorse this long wash-out because of the clear safety signals, lack of clinical data, and unknown immunological effects in pregnancy. If a pregnancy exposed to CLAD occurs, identical management as with S1PRMs applies.

Due to the lack of clinical/preclinical data for breastfeeding and its risk for accumulation in the breastfed infant, breastfeeding should be withheld for one week after the last CLAD administration [97,98]. Therefore, temporary suspension of direct breastfeeding and alternative feeding options (e.g., prepumped) need to be considered. As a precautionary measure, this option should be retained for pwMS with a high risk for disease activity [97]. If the pwMS decides not to breastfeed, an immediate treatment restart is possible.

Due to the potential mutagenicity of CLAD (disruption of DNA synthesis/repair by incorporation into DNA), an effect on spermatozoid genetic material is possible [11]. Therefore, the CH SmPC stipulates a wash-out of 6 months before the male pwMS can father a child. This is a conservative approach, as an interval of at least 3 months (one spermatogenesis cycle) between stopping CLAD and conception could be regarded as safe. Nevertheless, six months, as recommended by the label, should be targeted.

Recommendation: CLAD is not a treatment option in pregnancy because of the teratogenic effects observed in the preclinical models and the absence of human safety data in pregnancy. Breastfeeding should be withheld for one week after the last dose of cladribine. As it is a pulsed therapy that is administered over 2 years, we recommend completing the two cycles six months before family planning. In both women and men, contraception should be used for six months after the last CLAD dose.

4.3. Monoclonal Antibodies

Placental transfer of maternal immunoglobulin G (IgG) to the newborn occurs by means of complex transport mechanisms from \sim 13–14 weeks of pregnancy onwards [153,154]. Thus, passage of the placental barrier and, therefore, a direct effect on the newborn is unlikely in the first trimester. The maximum concentration is reached after the 35th week of pregnancy, and IgG1 is transported most effectively (IgG1 > IgG4 > IgG3 > IgG2) [155].

During breastfeeding, immunoglobulins such as mAbs can be passively excreted into the breast milk up to two weeks after delivery when the woman produces colostrum [156]. In addition, the gastrointestinal tract of the newborn is immature and less acidic; therefore, the bioavailability of mAbs will be higher. Therefore, mAbs should only be used in the first two weeks of breastfeeding after delivery if there is an absolute clinical need. If the pwMS has been treated with a mAb shortly before delivery, a higher concentration due to in utero exposure is to be expected anyhow. After that, passive transfer no longer occurs due to the large molecular size, and active transfer occurs only to a very small extent via Fc receptor-mediated processes [157,158]. Most therapeutic mAbs have very poor oral bioavailability, and in previous studies on various mAbs, only very low antibody concentrations could be detected in newborns after breastfeeding [111,118,159,160].

4.3.1. Natalizumab (Tysabri[®]) (Intravenous and Subcutaneous)

In line with the placental transfer characteristics of mAbs thus far, there are no clinical warning signs for first-trimester use [102–106]. However, if administered in the third trimester, hematologic changes in the newborn are possible [106–108]. Assessment of the use of natalizumab (NTZ) during pregnancy mirrors the complex benefit–risk assessment both for the fetus but also for pregnant pwMS. NTZ is a potential option for pwMS of childbearing age with a wish to conceive. The risk of rare but potentially severe progressive multifocal leukoencephalopathy needs to be taken into account (risk stratification according to anti-JCV-antibody index, length of treatment, and prior immunosuppressant use).

NTZ should not be discontinued without a bridging treatment plan in any patient. Especially in highly active RRMS, which predicts relapses during pregnancy or the postpartum phase in this vulnerable patient group [127,130,161], treatment continuation or bridging should be recommended (Table 1). NTZ can, thus, be discontinued before pregnancy with bridging to another high-efficacy treatment (such as ocrelizumab), e.g., in patients who are anti-JCV-positive or do not wish to continue NTZ during pregnancy; alternatively, NTZ can be continued during pregnancy [33,162].

Upon NTZ discontinuation, there is the risk of potentially severe rebound disease activity (ranging from 8% to 22% of pwMS) after discontinuation, which commonly occurs after 12–16 weeks [33,105]. Risk factors for disease reactivation after NTZ discontinuation should be evaluated (e.g., younger age, higher number of relapses, and gadolinium-enhancing lesions before treatment starts [20]). Should one, nevertheless, decide to discontinue NTZ, it is recommended to maintain high clinical vigilance and plan for a rapid restart after delivery [33,101].

If NTZ is continued during pregnancy, infusions can be scheduled according to an extended interval dosing (EID) regimen (e.g., every six weeks) [33,163]. The last infusion should be planned around 34 weeks of gestational age if MS activity allows (i.e., three half-lives before 40 weeks of gestation, corresponding to 94% NTZ elimination) to simultaneously minimize hematologic complications, decrease relapse rate, and avoid rebound disease activity. Specialist obstetrical surveillance should consider potential increased maternal–fetal infectious risk (e.g., listeriosis, CMV, toxoplasmosis). At birth, a neonatal hematological assessment should be planned, especially in the case of treatment beyond the second trimester. In the case of exposure in the third trimester, hematological changes (anemia, thrombocytopenia) in the newborn are to be expected and can outlast the full elimination of the drug [33]. However, these usually normalize by the fourth postpartum month [107]. In addition, neonates exposed to NTZ can have a slightly elevated likelihood of being small for gestational age, irrespective of the timing of NTZ discontinuation [33]. In case of NTZ exposure during pregnancy, in addition to an obstetrician/feto-maternal medicine specialist, we recommend co-management by an experienced neonatologist in the setting of a specialized MS center harboring all interdisciplinary facilities.

NTZ is excreted in low amounts in breast milk and has poor oral bioavailability beyond the colostrum phase; thus, significant systemic exposure in the breastfed infant is not expected [109–111]. In addition, the available limited clinical data, thus far, show no warning signs (Table 2). If the pwMS decides to breastfeed and the risk of disease activity is considered high, treatment during breastfeeding could be evaluated due to the very low RID and poor oral bioavailability [109–111]. If the pwMS decides not to breastfeed, NTZ should be restarted immediately after delivery.

Recommendation: The safety profile of NTZ in pregnancy makes it a first-choice drug in pwMS during pregnancy until the 34 weeks of gestational age when NTZ was the appropriate treatment beforehand. NTZ can also be used if the clinical situation requires intensification of previous immunotherapy during pregnancy. NTZ can be evaluated during breastfeeding because the very low RID and poor oral bioavailability suggest limited exposure of the infant. In men, NTZ can be used without restriction.

4.3.2. Ocrelizumab (Ocrevus®)

Thus far, no clinical warning signs for first-trimester use exist [115–117,119]. However, if administered during the third trimester, hematologic changes are possible in the newborn [115]. It is an option for the pwMS of childbearing age, especially with a wish to conceive in the medium to long term.

If the risk for disease activity is not considered high, ocrelizumab (OCR) should be discontinued. The CH SmPC recommends a six-month wash-out before conception; however, given the half-life, this interval is conservative. For pwMS with a high risk of disease activity during pregnancy, a shorter wash-out window can be considered. To avoid OCR exposure during pregnancy, effective contraception is recommended at least up to 2 months after the last dose (5–7 half-lives = ~19–26 weeks; distributed as 7–14 pre-gestational weeks + 12 first weeks of pregnancy without expected placental transfer).

In individual cases with a high risk for disease activity, treatment continuation during pregnancy can be a treatment strategy, as also stated by other consensus groups [164]. This is, however, rare as there is no risk of rebound activity after stopping OCR. The last infusion could be planned around 28 weeks of gestation if MS activity allows (i.e., three half-lives before 40 weeks of pregnancy, corresponding to 94% OCR elimination). Specialized obstetrical surveillance should consider potential increased maternal–fetal infectious risk (e.g., listeriosis, CMV, toxoplasmosis). At birth, a neonatal hematological assessment should be planned, especially in the case of treatment beyond the second trimester. The newborn should be considered immunosuppressed during the 24 weeks following the last maternal infusion of OCR. However, if hematological changes occur, this time window may be extended, as the biological effect can last beyond the full elimination of the drug. In the case of exposure in the third trimester, hematological changes (B-cell depletion, possibly lymphopenia) in the newborn are to be expected, and co-management by an experienced neonatologist in the setting of a specialized MS center harboring all interdisciplinary facilities both for the mother and the newborn is recommended. Should B-cell depletion be detected, it should be discussed with the treating neonatologist to postpone live vaccines until B-cell levels have adequately risen.

As OCR is excreted in low amounts in breast milk and has poor oral bioavailability beyond the colostrum phase, significant systemic exposure in the breastfed infant is not expected [118]. In addition, the available limited clinical data, thus far, show no warning signs [111,118,119]. However, clinical data are sparse. If the pwMS decides to breastfeed and the risk of disease activity is considered high, treatment during breastfeeding could be evaluated due to the very low RID and poor oral bioavailability. One can monitor B cells in the breastfed baby if additional assurance is wanted. If the pwMS decides not to breastfeed, treatment should be restarted immediately after delivery, especially in cases with highly active disease.

Recommendation: The safety profile of OCR makes it a possible choice drug in pregnant pwMS when OCR was the appropriate treatment beforehand. In this patient population, OCR can be evaluated during breastfeeding because the very low RID and poor oral bioavailability suggest limited exposure of the infant. In men, OCR can be used without restriction.

4.3.3. Ofatumumab (Kesimpta®)

Generally, it is reasonable to assume a similar safety profile to other anti-CD20 mAbs (e.g., ocrelizumab). Data are sparse, but, thus far, there are no clinical warning signs for first-trimester use [121]. If administered during the third trimester and extrapolating data from other anti-CD20-depleting treatments, hematologic changes are possible. Due to insufficient data and its shorter peripheral B-cell depletion in comparison to ocrelizumab, it is not clear if ocrelizumab and ofatumumab (OFA) provide similar (partial) protection during pregnancy [120]. OFA is an option for the pwMS of childbearing age, especially with a wish to conceive in the medium to long term.

According to the CH SmPC, OFA should be discontinued six months before trying to conceive [120]. Given the half-life, this interval is conservative. Especially for pwMS with a high risk of disease activity during pregnancy, a shorter wash-out window can be considered. To avoid exposure during pregnancy, a wash-out phase of 80–112 days (half-life 16 days) can be considered. This wash-out would allow OFA to be discontinued at the diagnosis of pregnancy, given the first 12 weeks of pregnancy without expected placental transfer. An additional strategy to limit exposure during pregnancy is the synchronization of injection schedules with menses [162]. In high-risk disease activity cases, continuation of OFA during pregnancy is a possible option. However, thus far, few data on safety outcomes in this situation are available. Therefore, alternative high-efficacy treatment strategies with more abundant evidence (see above) may be considered. In case of continuation of treatment during pregnancy, specialized gynecological/obstetrical management identical to ocrelizumab applies.

Beyond the colostrum phase, OFA has a poor oral bioavailability and is not expected to lead to significant systemic exposure in breastfed infants [120]. However, safety data on breastfeeding are limited [120]. Until more data become available, OFA should be used during breastfeeding if the clinical need is evident and other high-efficacy treatments (ocrelizumab, natalizumab) are not feasible. If the pwMS decides not to breastfeed, restarting shortly after delivery is recommended.

Recommendation: Due to limited data, OFA is only an option during pregnancy if therapeutic alternatives (e.g., ocrelizumab and natalizumab) with more evidence in pregnancy are not feasible. OFA should only be used during breastfeeding if the clinical need is appropriate and alternatives with more data are not feasible. In men, OFA can be used without restriction.

4.3.4. Alemtuzumab (Lemtrada®)

Preclinical data show safety signals at supratherapeutic doses [12]. However, clinical data are sparse. As this drug is only given during short cycles over two subsequent years with long intervals in between (pulsed treatment), it can be an option for pwMS in childbearing age with highly active MS (in the approved indication), especially with a wish to conceive in the long/medium term. Due to general safety aspects and other available alternatives, treatment with alemtuzumab (ALE) is generally not an attractive alternative during pregnancy.

Due to the fact that ALE is considered a third-line treatment and is an immune reconstitution therapy (IRT) without a short-term waning of treatment effects, we endorse the conservative wash-out period according to CH SmPC (4 months) in case of a planned pregnancy. If, on very rare occasions, it is continued during pregnancy, a neonatal hematological assessment should be planned at birth, especially in the case of treatment beyond the second trimester, to assess the immunological status of the newborn. In the case of exposure in the third trimester, hematological changes in the newborn are to be expected and can outlast the full elimination of the drug. If exposure occurs by the third trimester, we recommend co-management by an experienced neonatologist in the setting of a specialized MS center harboring all interdisciplinary facilities.

There is a risk of autoimmune thyroid disease (42%) up to six years after the last ALE cycle [165]. Maternal hypothyroidism can lead to growth and mental retardation in the newborn, in addition to an increased risk of miscarriage, preterm birth, and preeclampsia. Thyroid antibodies can cross the placenta and lead to neonatal Graves' disease [166]. Hence, scheduled regular monitoring of thyroid parameters (monthly for up to 4 years after the last infusion) must be followed strictly.

ALE has poor oral bioavailability beyond the colostrum phase and is not expected to lead to significant systemic exposure in the breastfed infant [12]. However, no safety data on breastfeeding are available. Until more data become available, ALE should not be used during breastfeeding. If the pwMS decides not to breastfeed and the next ALE cycle is needed, treatment should be initiated shortly after delivery.

Recommendation: Independent of pregnancy, ALE is considered a third-line treatment. Due to the absence of data in pregnancy and possible neonatal hematological toxicity, ALE should not be used during pregnancy unless in situations with no other therapeutic option. We do not consider ALE a suitable immunotherapy during breastfeeding. In men, ALE can be used without restriction.

Final comment

Managing family planning, pregnancy, and lactation in multiple sclerosis presents a unique challenge for healthcare professionals. Comprehensive interdisciplinary pre-conceptual counseling should be provided, covering treatment options and discussing the optimal timing for pregnancy. A joint assessment of the benefits and risks concerning disease activity and ongoing immunotherapy is crucial. It is essential to collaborate with an MS-specialized center and a fetomaternal center that offers interdisciplinary care, working closely with specialized obstetrics and neonatology teams for off-label decisions, particularly if immunotherapy continues during pregnancy. In addition, advice from specialized clinical pharmacologists/pharmacists should be sought. As current approvals are conservative due to limited data, frequent updates are needed as more information becomes available. Until then, off-label prescription during pregnancy and breastfeeding remains the treating physician's responsibility and should be limited to cases where the benefits outweigh the risks. Lastly, in the benefit–risk assessment, the palpable threat of undertreatment of active MS must be accounted for.

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Appendix A

Use during pregnancy/lactation according to CH SmPC

Interferon beta (IFNB) preparations (Avonex[®], Betaferon[®], Plegridy[®], Rebif[®])

Approval in Switzerland (selected aspects; for complete text, see [26–29]): If clinically necessary, Avonex[®]/Betaferon[®]/Plegridy[®]/Rebif[®] may be used during pregnancy. Avonex[®]/Betaferon[®]/Plegridy[®]/Rebif[®] can be used during breastfeeding.

Glatiramer acetate (Copaxone[®], Glatiramyl[®])

Approval in Switzerland (selected aspects; for complete text, see [55,167]): As a precaution, use of Copaxone[®]/Glatiramyl[®] during pregnancy should be avoided unless the benefit to the mother outweighs the risk to the fetus. Copaxone/Glatiramyl[®] can be used during breastfeeding.

Teriflunomide (Aubagio[®])

Approval in Switzerland (selected aspects; for complete text, see [13]): Teriflunomide must not be used in pregnant women. This also applies to women of childbearing potential who are not using reliable contraception during treatment. You may only become pregnant when the active substance concentration in the blood has fallen below 0.02 mg/l. Because many drugs are excreted in breast milk in humans, and because of potentially serious adverse events in infants, mothers taking teriflunomide must not breastfeed.

Dimethyl fumarate (Tecfidera[®])/diroximel fumarate (Vumerity[®])

Approval in Switzerland (selected aspects; for complete text, see [72,79]): Tecfidera[®]/Vumerity[®] should only be used during pregnancy if the patient's clinical findings absolutely require treatment and the potential benefit justifies the potential risk to the fetus. It must be decided on an individual basis whether breastfeeding or treatment with Tecfidera[®]/Vumerity[®] should be interrupted.

Fingolimod (Gilenya[®])

Approval in Switzerland (selected aspects; for complete text, see [10]): Women should not become pregnant during treatment and an effective method of contraception must be used. Information about the potentially serious consequences for the unborn child and the need for effective contraception during treatment and for 2 months after stopping treatment with Gilenya[®] must be provided. Fingolimod is contraindicated during breastfeeding.

Ozanimod (Zeposia[®])

Approval in Switzerland (selected aspects; for complete text, see [87]): Zeposia[®] is contraindicated during pregnancy and is not recommended for women of childbearing age who are not using effective contraception. Zeposia[®] should be discontinued 3 months before a planned pregnancy. A decision must be made as to whether breastfeeding should be interrupted or whether treatment should be discontinued.

Ponesimod (Ponvory[®])

Approval in Switzerland (selected aspects; for complete text, see [89]): Ponvory[®] is contraindicated during pregnancy and is not recommended for women of childbearing age who are not using effective contraception. Zeposia[®] should be discontinued 3 months before a planned pregnancy. Ponvory[®] should not be used during breastfeeding.

Cladribine (Mavenclad[®])

Approval in Switzerland (selected aspects; for complete text, see [11]): Pregnancy must be prevented by using effective contraception during treatment with cladribine and for at least 6 months after the last dose. Pregnancy must be prevented during treatment with Mavenclad[®] and for at least 6 months after the last dose by the use of a reliable method of contraception. In view of the potential for serious adverse effects in breastfed infants, breastfeeding is contraindicated during treatment with Mavenclad[®] and for 1 week after the last dose.

Natalizumab (Tysabri[®])

Approval in Switzerland (selected aspects; for complete text, see [100]): Tysabri[®] should not be used during pregnancy unless the patient's clinical findings necessitate treatment with Tysabri[®]. Tysabri passes into breast milk. The effect of natalizumab on neonates/infants is unknown. Breastfeeding should therefore be discontinued during treatment with Tysabri[®].

Ocrelizumab (Ocrevus[®])

Approval in Switzerland (selected aspects; for complete text, see [114]): Therapy should not be started during pregnancy. Ocrevus[®] should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. Women of childbearing potential should use reliable contraception during Ocrevus[®] treatment and until 6 months after the last Ocrevus[®] infusion. Women should be advised to discontinue breastfeeding during ocrelizumab therapy because human IgG is excreted into breast milk and it is not known what the potential for B-cell reduction is with Ocrevus[®] intake.

Ofatumumab (Kesimpta[®])

Approval in Switzerland (selected aspects; for complete text, see [120]): Kesimpta therapy must not be initiated during pregnancy. Kesimpta[®] should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. Women of childbearing potential should use effective contraception while taking Kesimpta and for 6 months after the last dose of Kesimpta[®]. The benefits of breastfeeding for the development and health of the breastfed infant should be considered along with the clinical benefits of Kesimpta[®] to the mother and the potential adverse effects of Kesimpta[®] on the breastfed newborn/infant.

Alemtuzumab (Lemtrada[®])

Approval in Switzerland (selected aspects; for complete text, see [12]): Lemtrada® should not be used during pregnancy unless clearly necessary. However, therapy must not be started during pregnancy. Therefore, women of childbearing potential must use a reliable method of contraception during a Lemtrada® treatment cycle and for 4 months after the treatment cycle. Breastfeeding should be discontinued during a treatment cycle with Lemtrada® and for 4 months after the last infusion of a treatment cycle.

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