Universidade de Lisboa

Faculdade de Farmácia

Risk Mitigation strategies for multiple sclerosis medicines use in pregnancy

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Monografia orientada pelo Professor Doutor João Pedro Fidalgo Rocha,
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Resumo

A Esclerose Múltipla é uma doença neurológica que afeta principalmente jovem adultos em idade reprodutiva, com uma proporção de mulheres para homens de aproximadamente 3: 1.

Atualmente, há um número crescente de Medicamentos Modificadores Da Doença disponíveis para o tratamento da Esclerose Múltipla, o que significa que os profissionais de saúde que lidam com Esclerose Múltipla devem estar preparados para discutir assuntos de gravidez e fornecer aconselhamento apropriado para a utilização destes fármacos. Para o aconselhamento da doente com Esclerose Múltipla é fundamental reunir informações sobre os efeitos dos Medicamentos Modificadores Da Doença em questões relacionadas à gravidez, portanto, é importante classificar os tratamentos modificadores da doença de acordo com seu potencial de risco associado à gravidez e impacto no feto.

Como alguns tratamentos são contraindicados na gravidez, há necessidade de contracetivos; felizmente, a maioria dos métodos contracetivos parecem ser seguros para doentes com Esclerose Múltipla.

O interferão beta e o acetato de glatirâmero podem ser mantidos até que a gravidez seja confirmada e durante a gravidez após ponderação do risco-benefício individual. Além disso, em doentes com Esclerose Múltipla altamente ativa, o benefício de continuar o natalizumab durante a gravidez pode exceder o risco da recorrência da doença.

O efeito dos sintomas da Esclerose Múltipla, como Espasticidade, Fadiga e Dificuldade em Andar, na qualidade de vida pode ser profundo, e o tratamento farmacológico é um componente essencial na gestão destes sintomas. No entanto, estes tratamentos só devem ser utilizados durante a gravidez se o possível benefício superar o risco para o feto.

Palavras-chave: Esclerose Múltipla; Gravidez; Medicamentos Modificadores Da Doença

Abstract

Multiple sclerosis is a neurologic disease affecting mainly young adults of reproductive age, with approximately a 3:1 female-to-male ratio.

Currently there are a growing number of disease-modifying drugs available for the treatment of Multiple Sclerosis, meaning that healthcare providers who deal with Multiple Sclerosis must be prepared to discuss pregnancy issues and provide appropriate counselling on the use of these drugs. For the counselling of Multiple Sclerosis patients, gathering information on the effects of disease-modifying drugs on pregnancy-related issues is critical. Therefore, it is important to classify Disease-modifying treatments according to their potential for pregnancy-associated risk and impact on foetal outcome.

As some treatments are contraindicated in pregnancy, there is a need for contraceptives, luckily most methods of contraception appear to be safe for patients with Multiple Sclerosis.

Interferon beta and glatiramer acetate can be maintained until pregnancy is confirmed and during pregnancy after weighting the individual risk-benefit if continued. Furthermore, in patients with highly active Multiple Sclerosis, the benefit of continuing natalizumab throughout pregnancy may exceed the risk of recurring disease activity.

The effect of Multiple Sclerosis symptoms, such as Spasticity, Fatigue and Walking Impairment, on quality of life can be profound, and pharmacological treatment is an essential component in the management of these symptoms. However, these treatments should only be used during pregnancy if the possible benefit outweighs the risk to the foetus.

Keywords: Multiple Sclerosis, Pregnancy, Disease-modifying drugs

List of Abbreviations

MS- Multiple Sclerosis

QOL- Quality Of Life

CNS- Central Nervous System

DIT- Dissemination In Time

DIS- Dissemination In Space

CSF- Cerebrospinal Fluid

MRI- Magnetic resonance imaging

RRMS- Relapsing-Remitting Course

SPMS- Secondary Progressive Multiple Sclerosis

PPMS- Primary Progressive Multiple Sclerosis

CIS- Clinically Isolated Syndrome

DMTs- Disease Modifying Therapies

IUD- Intrauterine Device

IFN-β- Interferon-β

BBB- Blood Brain Barrier

GA- Glatiramer Acetate

UVB- Ultraviolet B Light

PRIMS- The Pregnancy in Multiple Sclerosis study

IFNs- Interferons

SC- Subcutaneous

IM- Intramuscular

APCs- Antigen Presenting Cells

VCAM- Vascular Cell Adhesion Molecules

VLA-4- Very Late Antigen-4

kDa- Kilodaltons

PEG- Polyethylene Glycol

FDA- Food and Drug Administration

DMF- Dimethyl fumarate

MMF- Monomethyl Fumarate

ICAM- Intracellular Adhesion Molecules

EMA- European Medicines Agency

tIS- Terminal Half-Life

S1P- Sphingosine 1-Phosphate

S1PR- Sphingosine 1-Phosphate Receptor

CYP2C9- Cytochrome P4502C9

IgG1- Immunoglobulin G1

GABA- Gamma-Aminobutyric Acid

4-AP- 4-Aminopyridine

NICE- National Institute for Health and Care Excellence

ADHD- Attention-Deficit Hyperactivity Disorder

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1 Introduction

Multiple sclerosis (MS) is the most common non-traumatic acquired disabling disease and the most frequent chronic neurological immune-mediated disorder to affect young adults.(1,2)

MS has a profound impact on patients' quality of life (QOL).(3) A number of factors have been identified as affecting QOL in patients with MS such as physical disability, progressive disease, fatigue, pain, cognition, anxiety, depression, as well as elevated suicide rates.(4,5)

A study done with an Italian cohort found that 1 out of 4 patients with MS has a concomitant medical condition at MS diagnosis, and 5% have 2 concomitant medical conditions, mainly expectedly other autoimmune diseases, specifically thyroid diseases, type 1 diabetes mellitus, and celiac disease, were the most common concomitant diseases.(6)

Multiple sclerosis is a complex neurodegenerative condition caused by immune system dysfunction that affects the central nervous system (CNS) and it is characterized by demyelination, chronic inflammation, neuronal and oligodendrocyte loss, and reactive astrogliosis.(7) There are an heterogeneous array of symptoms and signs because of differential involvement of motor, sensory, visual and autonomic systems.(8) Many of the clinical features of MS are not disease-specific, Lhermitte's symptom (an electrical sensation running down the spine or limbs on neck flexion) and the Uhthoff phenomenon (transient worsening of symptoms and signs when core body temperature increases) are particularly characteristic of MS.(9)

The diagnosis of MS is still mainly clinical in spite of advances in diagnostics and the availability of several radiological and neuroimmunological surrogate markers.(10) The basis for diagnosis focuses on comprehensive history taking and neurological examination to determine dissemination in time (DIT) and space (DIS) of certain clinical symptoms and signs as well as excluding mimickers.(10) Many diseases have similar clinical and imaging findings, nevertheless there are distinguishing characteristics for each disease that must be considered, such as clinical history, age, race or ethnicity, sex, patterns on imaging, travel history, and laboratory findings (Cerebrospinal fluid [CSF]), antibody testing, biopsy, genetic testing).(11) Blood and

CSF analyses can be used to investigate certain inflammatory or infectious disorders (e.g., systemic lupus erythematosus and neuroborreliosis) that are often part of the differential diagnosis.(12)

DIS is characterized by the occurrence of one demyelinating lesion in at least two of four areas (periventricular, juxtacortical, infratentorial, and spinal), whereas DIT can be proven by simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time or the presence of a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI (Magnetic Resonance Imaging), with reference to a baseline scan, irrespective of the timing of the baseline MRI.(10)

Multiple sclerosis has various moments in the progression of the disease such as asymptomatic, prodromal and symptomatic phases.(13) Moreover MS is thought to appear before clinical symptoms are apparent to the patient.(13,14)

MS diagnosis can be established based on at least two typical clinical attacks or a single typical demyelinating event along with evidence of DIS and DIT by MRI.(10) MS can be described as having three main stages, the first a pre-clinical stage, in which a combination of genetic and environmental factors trigger the disease, the second a relapsing-remitting (RRMS) clinical stage, which is characterized by distinct, self-limited phases of neurologic dysfunction, such as optic neuritis, sensory disturbances, or disturbances in motor and cerebellar function (this inflammatory stage may only be evident by MRI imaging) intertwined with periods of neurological stability, then a progressive clinical stage in which neurologic dysfunction progressively worsens, affecting, mainly, a patient's gait.(14)

A relapsing-remitting course is present in approximately 85-95 percent of patients.(3) Around 60-70 percent of RRMS patients within 20-25 years after this course transform into a secondary progressive multiple sclerosis (SPMS) disease course, which is characterized by progressive neurological decline.(15) Nevertheless MS can also assume a progressive course, from the onset, characterized by a steadily increasing neurological decline (primary progressive MS [PPMS]).(3) In most cases from MRI imaging studies it can be inferred that primary progressive MS is basically the secondary progressive form, in which the relapsing stage was not clinically apparent.(14) When the disease begins as primary progressive MS it represents a unique

subtype of MS, even though the mechanisms that drive both primary and secondary progressive MS are thought to be the same.(14)

MS is suspected when a patient appears with a clinically isolated syndrome (CIS), which can be mono- or polysymptomatic according to the location of the eloquent lesion(s).(13) Clinically isolated syndrome is the initial presentation in 80% of MS cases.(8) CIS is an acute clinical attack affecting one or more CNS sites and can convert to relapsing remitting MS.(8) Most frequently CIS presentations involve a single optic nerve, the spinal cord, or the brain stem, though other isolated syndromes can occur, such as those that affect the cerebral hemispheres (e.g., hemianopsia).(16) If the patient is later diagnosed with MS (by meeting DIS and DIT and ruling out other possible diagnoses), the CIS was that patient's first attack.(17)

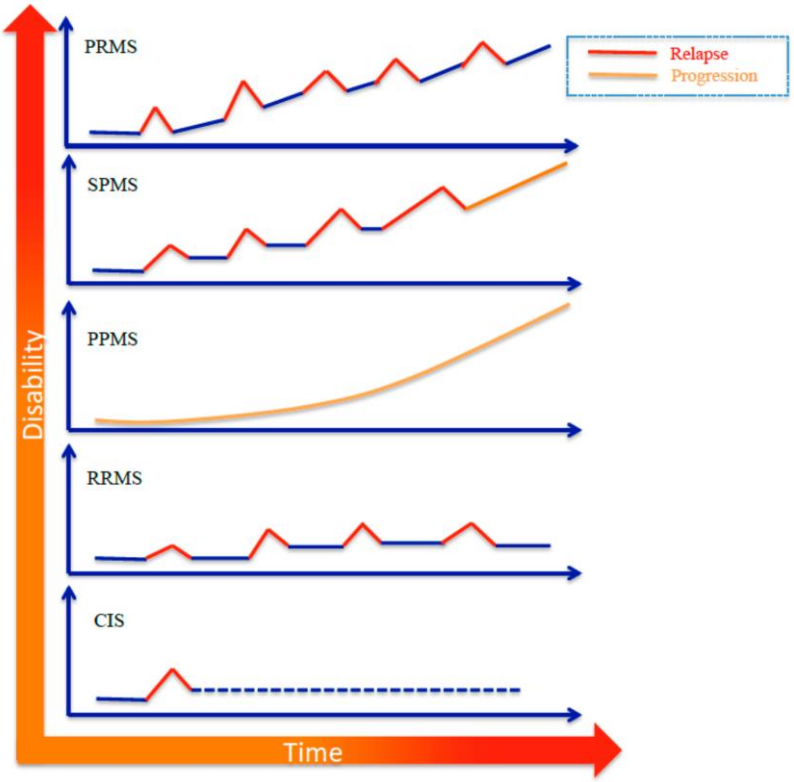

Figure.1 Symptom patterns that define the subtypes of multiple sclerosis (MS). CIS, clinically isolated syndrome; RRMS, relapsing/remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PRMS, progressive-relapsing multiple sclerosis.(18)

The treatment for MS can be categorized into acute relapse management, disease-modifying treatments (DMTs) that are used to reduce inflammatory disease activity and its long-term clinical consequences and symptomatic treatments, used for short-term improvement of MS symptoms such as fatigue, pain and spasticity.(5,8,19)

Relapses are the onset of new signs and symptoms caused by a new focal demyelinating lesion in the central nervous system that usually resolves, partially or entirely, within days to weeks, it typically occurs in the absence of an infection and after symptoms have been stable for at least one month.(20)

An exacerbation is a worsening of existing signs and symptoms caused by a focal demyelinating lesion in the central nervous system that usually resolves, partially or completely, within days to weeks. Exacerbation can also refer to a relapse characterized by a significant worsening of an existing symptom.(20)

Current preventive disease-modifying therapies main therapeutic aim is to prevent or postpone long-term disability, reducing the frequency and severity of MS attacks.(21,22)

DMTs may be used as sequential monotherapies or as part of escalation or induction strategies.(22) An escalation strategy is when the patient starts with a safe but moderately effective DMT, typically Interferon-β (IFN-β), glatiramer acetate (GA), teriflunomide or Dimethyl Fumarate (DMF), and in case of intolerable adverse effects switch to another first-line DMT, or in patients with new relapses or MRI lesions to a more effective DMT (second-line or third-line therapies).(5) While an induction strategy is when high efficacy drugs are used earlier in disease to possibly prevent disability increase, despite their significant side effect profile. (8)

Symptomatic therapies are often not MS-specific and refer to pharmaceutical and physical therapies that target neurological dysfunction symptoms arising due to CNS damage.(13) Symptomatic treatment is critical in the care of MS patients in order to improve the quality of life and the ability to work.(23)

MS is not in its essence an inherited disorder.(24) The etiopathogenesis of MS is likely based on the intricate interaction between genetic factors and environmental triggers.(24) Many genes modestly increase disease susceptibility, the strongest genetic risk factor is linked to HLA (HLA DRB1*15), in addition to many well-established environmental factors, in particular the lack of vitamin D, the exposure to ultraviolet B light (UVB), Epstein–Barr virus infection, obesity and smoking.(24,25)

2 Epidemiology

Around 2.3 million people worldwide are affected by MS and its prevalence is surprisingly heterogeneous, ranging from 50 to 300 patients per 100 000 inhabitants.(3,26)

Multiple sclerosis has an average onset age of approximately 30 years, while research from various populations suggest earlier presentations.(27)

The increasing prevalence and incidence of MS, with a 2-3-fold occurrence of cases in females versus males, suggests a large and increasing burden of MS among women of childbearing age.(27)

MS takes a more severe course in patients of the male sex who present MS in their forties and fifties or patients who present during childhood or adolescence.(11)

The prototypic patient with Multiple Sclerosis is a woman of reproductive age, young women (20 to 40 years), which means that pregnancy and family planning are considerable concerns for women with MS.(28,29)

Compared to women without MS, MS per se does not appear to carry a greater risk of adverse pregnancy outcomes (no increased risk for miscarriage or congenital malformation).(27) However, there is a tendency towards assisted delivery/caesarean section, studies suggest that women with MS are more likely to require an instrumental delivery (vacuum extraction), most likely due to a higher risk of fatigue and exhaustion among MS patients; another potential predisposing factor could be MS-related disability leading to perineal weakness and/or spasticity.(27,29,30)

Regarding childbirth there are no contraindications to Caesarean Section or Vaginal Delivery, thus the decision relating to the mode of delivery is normally based on obstetrical indications rather than neurological.(28,31,32)

During pregnancy, women's immune system are reported to be more immunotolerant due to a shift in the ratio of T helper 1 and 2 cells, mediated by high levels of estrogens, particularly estradiol, in addition to other important hormones including progesterone and androgens.(33)

Pregnancy in MS does not appear to increase the risk of exacerbations; in fact, a reduction in disease activity, both in the reduction of MS risk and a delay in MS onset,

appears coincident with increasing concentrations of gestation-related steroid hormones, most noticeable during the final trimester, although the progression of longer-term clinical disease is unaffected.(1,27,33) Throughout the duration of an entire individual pregnancy, from pre- to post-pregnancy, the relapse risk appears to be comparable to the non-pregnant state.(34) A study published in 1998 called The Pregnancy in Multiple Sclerosis study (PRIMS) is still a reference in terms of the natural progress of MS in pregnancy.(35) The PRIMS studied 254 women with multiple sclerosis during 269 pregnancies in 12 European countries, the women were followed during their pregnancies and for up to 12 months after delivery, between 1992 and 1995.(36) In this prospective study the frequency of relapses of multiple sclerosis reduced during pregnancy, particularly during the third trimester, and increased in the first three months postpartum, as compared with the rate during the year before pregnancy.(36)

Due to the age at which patients usually become pregnant, the most frequent presentation of the disease is RRMS, as well as SPMS and PPMS are very rare phenotypes during pregnancy.(35)

3 Contraception in Multiple Sclerosis Patients

Patients with MS of childbearing age may choose to delay pregnancy, choose not to have children, or consider their families complete, therefore it is important to be familiar with any potential for drug–drug interactions between contraceptive methods and DMTs or any other treatments.(37) No known drug–drug interactions between currently available DMTs and contraceptives have been reported for therapies other than teriflunomide.(37,38) Following repeated doses of teriflunomide there was an increase in ethinyloestradiol and levonorgestrel peak serum concentrations and total drug exposure.(38) Although this interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, it should be considered when selecting or adjusting oral contraceptive treatment used in combination with teriflunomide.(38)

The optimal time for a patient with MS to conceive should be up to consideration individually, based on MS activity, treatment response, plus the resources available to manage the challenges of early child raising.(39) The neurologist should be consulted, but also members of the interdisciplinary team, which should include an obstetrician-gynaecologist and a psychologist/psychiatrist.(40) Any comprehensive treatment plan for patients of reproductive age with MS should include regular counselling on the use of effective contraceptives to optimally time desired pregnancies and avoid unwanted pregnancies.(39) When discussing pregnancy disease course and activity must be considered, to allow the determination the course and MS activity a year interval is the ideal time between the time of diagnosis and the decision-making about a planned pregnancy.(40,41)

The choice of the appropriate contraception method will depend on factors such as effectiveness, safety, availability, and acceptability; particularly for patients with MS there are additional issues as difficulty swallowing pills or manual dexterity needed for placing vaginal rings and barrier methods.(39)

Based on current evidence most methods of contraception appear to be safe for patients with MS.(39) There are no contraindications for the use of Intrauterine Devices (IUD), levonorgestrel-releasing intrauterine systems, progestogen-only pills, agents containing oestrogens and progestogens such as contraceptive vaginal rings containing hormones, oral contraceptive pills, and transdermal contraceptive patches.(40) The only

contraindication is for the use of combined hormonal contraceptives by women with MS with prolonged immobility due to concerns about possible Venous thromboembolism risk.(39)

There is a need for highly effective contraception during treatment with DMT that are potentially teratogenic.(40) For patients with MS taking potentially teratogenic medications, highly effective contraceptive methods that are long-acting, such as IUD and implants, might be the best option to avoid unplanned pregnancies.(39)

4 Disease Modifying Therapies During Pregnancy

MS treatments consist of drugs targeted to prevent relapses of the disease, and consequently, the progression of disability, these medications are called “disease-modifying therapies”.(42) The introduction of several oral DMTs over the last decade represents a significant advance in the treatment of Multiple Sclerosis, particularly in terms of increased patient satisfaction and improved treatment adherence.(43)

A good response to DMT is characterized when there is ‘no evidence of disease activity’ in both the clinical (no MS relapses or disability progression) and MRI (no new T2 lesions or atrophy) parameters for at least two years.(8,40)

The main issue related to pregnancy in multiple sclerosis patients is the pharmacotherapy, specifically the use of disease-modifying therapies.(25) Due to its theoretical risk for relapses to occur in the early phases of pregnancy, it is important to provide a recommendation in the clinical setting concerning treatment.(33) Unfortunately currently there is no consensus in the literature regarding MS treatment up to and during pregnancy.(44)

The selection of DMT should be a joint decision between physicians and patients.(45) Preferably, clinicians and their patients with MS should discuss family planning as early as possible in the course of treatment, allowing patients to make informed decisions about their medication choices during pregnancy while maintaining optimal disease protection throughout pregnancy and during the postpartum period.(46) The decision to continue DMT during pregnancy depends on disease severity and the DMT in question.(24)

In a study intended to describe dispensing patterns and the safety of DMTs during pregnancy, with a cohort of 984 058 pregnant women, 1649 women with MS were identified. This study revealed that the prevalence of DMT dispensing was 35% before pregnancy, dropped during pregnancy, and then returned to pre-pregnancy levels in the postpartum. This may be a result of hesitancy of physicians to prescribe DMTs, patients to fill the prescription, or related to the previously mentioned decline of disease activity during pregnancy.(47)

Whilst the amount of data available on DMT safety in people who become pregnant is expanding, few DMTs are currently considered completely safe for use during pregnancy.(24)

The relatively modest efficacy of many of the early disease-modifying drugs, interferon-beta preparations and glatiramer acetate, along with limited evidence of safety in pregnancy, has previously led many women to defer starting disease-modifying drugs until after they had completed their families.(2) However early intervention with disease-modifying drugs has been shown to reduce/delay long-term disability caused by neuroaxonal damage in relapsing-remitting MS.(48) A DMT should be prescribed as soon as a patient has been diagnosed with RRMS or CIS to reduce the risk of disease progression.(5)

4.1 Interferon β

Interferons (IFNs) are a group of proteins, endogenous cytokines, that normally produce cells in response to viral infections and other stimuli, regulating the immunological response, and are important components of the innate immune system.(49–51)

The fact that IFNs have antiviral properties was what prompted initial interest as a potential therapeutic option for MS.(52) Interferons were first described in 1957 and named for its ability to interfere (clash) with the viruses.(53)

Beta-Interferons inhibit the activation and proliferation of T-lymphocytes by down-regulation of major histocompatibility complex class II expression on antigen presenting cells (APCs) as well as by impairing the interaction of CD40L and CD28 on T cells.(45)

By increasing vascular cell adhesion molecules (VCAM) that block leukocyte adhesion to the endothelium via very late antigen-4 (VLA-4), Interferon- β (IFN-β) also impacts the Blood Brain Barrier (BBB).(45)

IFN-β was the first drug approved for the treatment of MS, and it is available in two varieties: IFN β-1b and IFN β-1a.(54) There are four different interferon preparations available for the treatment of MS, subcutaneous (SC) IFN β-1b, intramuscular (IM) IFN β-1a, SC IFN β-1a and SC pegylated form of IFN- β-1a.(54) All of them must be administered by injection (either every other day or three times a week SC, weekly IM, or every fortnight SC).(54)

Current clinical treatment guidelines consider the option for patients with high risk of reactivation the use of interferon or glatiramer acetate until pregnancy is confirmed.(55) Furthermore in specific cases, this treatment may be continued during pregnancy.(2,55)

In Europe, currently there is not a contraindication for the prescription of IFN-β, the risk benefit relation should be discussed with the patient, as such if clinically needed, the use may be considered during pregnancy.(56) The Summary of Product Characteristics was updated following the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issuing a positive opinion based on more than 4,000 pregnancy outcomes from registries and post-marketing experience indicating no increased risk of major congenital anomalies after preconception exposure to IFN-β or exposure during the first trimester of pregnancy.(57) However due to the fact that data were collected when IFN-β use was contraindicated during pregnancy, the treatment was likely interrupted when the pregnancy was detected and/or confirmed and the duration of exposure during the first trimester is uncertain.(57)

It is necessary to discuss with the patient the risks and benefits of maintaining treatment during pregnancy (and the potential for relapse from cessation of treatment from a patient with highly active MS).(27) If IFN-β is stopped during pregnancy, it will take several months to reach full efficacy when restarted and so may not reduce relapse rate during the first few months postpartum.(2)

A systematic analysis of 761 pregnancies exposed to IFN-β concluded that IFN-β exposure was neither associated with an increased teratogenic or abortive risk nor with an increased risk for caesarean sections.(58) After IFN-β exposure, however, lower mean birth weight (on average 213 g) and length (on average 1.6 cm) and a higher rate of preterm births could be observed.(58) These findings are consistent with the pharmacologically plausible safety of IFN-β exposure in early pregnancy and provide further reassurance that IFN-β treatment can be safely continued up until pregnancy.(58)

4.1.1 Interferon β-1b

IFN-β-1b was the first recombinant product to be approved for use in MS.(49)

A study containing the largest worldwide sample of patients exposed to IFN-β-1b during pregnancy reported in the global Bayer's pharmacovigilance database, did not

find an increase in the rate of abnormal pregnancy outcomes, as well as rates of spontaneous abortion and major or minor birth defects were not higher than background estimates from the general population.(59)

The Betaseron Pregnancy Registry was a voluntary, prospective, observational, exposure registration and follow-up study, that enrolled women with an existing pregnancy who had been exposed to IFN β-1b at any time after the first day of the last menstrual period, or during pregnancy but before any prenatal screening (e.g., ultrasound and amniocentesis).(60) The prevalence of spontaneous abortion in the Betaseron Pregnancy Registry was not significantly different from the estimate for the general population of the USA.(60) The Betaseron Pregnancy Registry did not find any patterns to suggest negative pregnancy outcomes associated with interferon β-1b exposure.(60) IFN-β-1b may be used during pregnancy if it is clinically necessary.(61)

IFN-β-1b injected subcutaneously has a half-life time of 5 hours.(58)

4.1.2 Interferon β-1a

IFN-β-1a is an intramuscular and subcutaneous product that is administered once a week.(52) A study assessing outcomes in women with MS who became pregnant while receiving SC IFN-β-1a therapy, using data from a global drug safety database, showed that the majority of pregnancies exposed to SC IFN-β-1a (76.2%) were associated with normal, live births.(60) The study showed that it is unlikely that there is an association between SC IFN-β-1a and spontaneous abortion as the percentage of pregnancies resulting in spontaneous abortions (11.5%), with or without foetal defects, was in line with the reported rate in the general population (known to be relatively common, 10–20% before 20 weeks of pregnancy).(60) The large size of the IFN molecule [approximately 23 Kilodaltons (kDa) for IFN-β-1a] may inhibit the degree to which IFN crosses the placental barrier, explaining why IFN-β1a appears to have no detrimental impact on pregnancy outcomes.(60)

The Food and Drug Administration (FDA) has awarded IFN-β 1a the pregnancy category B.(62)

According to the Summary of product characteristics of IFN-β-1a there is limited information available on its presence in breast milk, in addition to the fact that IFN-β is a macromolecule with limited oral bioavailability suggests that the levels excreted

in human milk are negligible and therefore, it is possible to consider breastfeeding under IFN-β.(56,58)

4.1.3 Pegylated interferon β-1a

The process of chemically conjugating polyethylene glycol (PEG) molecules to a biological product is known as pegylation.(63) PEG increases the size of a macromolecule, increasing its solubility, stability, and mobility in solution, slowing renal clearance, resulting in increases in exposure, elimination half-life, and maximal serum concentration, and possibly reducing receptor- or antibody-mediated clearance as well as proteolytic degradation.(63,64)

A pegylated form of IFN- β-1a was approved in 2014, reducing the frequency of administration to twice monthly, and as it is administered subcutaneously fewer skin reactions may occur than under weekly intramuscular administered preparations.(54,65)

Pegylated interferon β-1a may be used during pregnancy if it is clinically necessary.(61)

4.2 Glatiramer Acetate

Glatiramer acetate is an acid polymer synthesized by copolymerization of four naturally occurring amino acids, (glutamic acid, lysine, alanine and tyrosine), that reduces the activity of MS by promoting suppressor cells, expanding regulatory T cells and modifying APCs.(65)

There is insufficient evidence from preclinical animal studies with regard to the impact of GA on fertility, teratogenicity or foetal development; in humans, nearly all studies, with large sample size (>2000) in the manufacturers own pharmacovigilance data, found no association between negative pregnancy outcomes and the exposure to GA.(58) Glatiramer acetate is classified as a 'B' by the FDA for medication use during pregnancy, administration of GA by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on offspring development.(65) However as animal reproduction studies are not always predictive of human response, it should only be taken during pregnancy if needed, if the benefit to the mother outweighs the risk to the foetus.(24,65)

In comparison with DMT-unexposed women with MS, GA exposure during early pregnancy did not increase the risk for any adverse pregnancy outcome.(58) When

compared to MS patients who were not exposed to GA during pregnancy, after an average exposure of approximately 4 weeks, there was no significant increase in the risk of spontaneous abortion or the frequency of premature birth, as well as no significant differences in infant mean birth weight and length.(66)

When taking this agent, breastfeeding may be possible, but it should be subject to consideration with the patients in regard to the risks and benefits for themselves and their children.(27)

4.3 Mitoxantrone

Mitoxantrone is used to treat patients with worsening multiple sclerosis when no alternative treatments are available.(67) In patients with secondary (chronic) progressive, progressive relapsing or worsening relapsing remitting multiple sclerosis, mitoxantrone is prescribed to minimize neurologic dysfunction and/or the frequency of clinical relapses.(68)

Mitoxantrone interferes with DNA repair as an immunosuppressant and inhibits cellular migration, induces dendritic cell apoptosis, inhibits the function of B and T cells and inhibits myelin degradation mediated by macrophages.(45) Nevertheless, due to dose-related cardiac toxicity and hematologic side effects, it has fallen into disuse.(45)

Mitoxantrone has been identified as a cause for growth retardation and preterm birth in animals.(69) During pregnancy, this drug is contraindicated, due to its mechanism of action, as it is considered a possible human teratogen.(67,68) It is classified in the pregnancy category risk D by the FDA.(68) Spontaneous abortion and reduced foetal growth have been observed in new-borns of women with in utero mitoxantrone exposure for cancer treatment, and secondary amenorrhea can also be observed in women using mitoxantrone.(69) The manufacturer of Mitoxantrone advises that pregnancy tests should be done before each dose for people with multiple sclerosis who are biologically capable of becoming pregnant, and that the results be known prior to its administration.(68)

Patients of childbearing potential should use effective contraception during therapy and for at least 4 months after cessation of treatment.(70)

Mitoxantrone has a half-life of 3 days. (69)

4.4 Teriflunomide

Teriflunomide is a once-daily oral agent that has been licensed in the European Union since August 2013 for the treatment of adult patients with RRMS.(71)

Teriflunomide is an active metabolite of leflunomide, it is a reversible inhibitor of dihydroorotate dehydrogenase, an enzyme involved in de novo pyrimidine synthesis for DNA replication, thus decreasing B- and T-cell activation and proliferation.(45)

So far, the teratogenic risk of teriflunomide in humans is unknown.(58) If differences in the enzyme affinity between animals and humans can account for the higher risk of teratogenicity in animal as in humans is hypothetical.(58) Doses below those clinically used were linked to teratogenicity and embryo deaths in various species animal studies.(72) Teriflunomide is contraindicated in patients who are pregnant or of childbearing potential if not using reliable contraception.(58,71) People with multiple sclerosis who are biologically capable of becoming pregnant must use effective contraception while being treated with teriflunomide.(58)

Although the half-life of teriflunomide is 16-18 days, it can remain up to 2 years in the system, pregnancy is not desirable until teriflunomide treatment is completed and concentration is below 0.02 mg/mL.(58,72) If women plan to become pregnant teriflunomide treatment should be stopped and an accelerated elimination procedure should be initiated and serum level controlled (<0.02mg/mL).(58) In the event of an unintended pregnancy a sudden accelerated plasma elimination procedure (with plasma level control) is essential.(58) In these cases of accidental conception the patient would benefit from quick elimination protocol with cholestyramine or activated charcoal administration for a few days to reduce teriflunomide concentration to 0.02 mg/mL.(72) As well as an organ screening ultrasound is recommended.(58)

Women should not breastfeed due to the excretion of teriflunomide into breast milk.(72)

4.5 Dimethyl fumarate

Dimethyl fumarate (DMF), a second-generation fumaric acid, is an oral immunomodulatory DMT approved in the European Union, the United States of America and in several other countries for the treatment of RRMS patients.(43,51) DMF is recognized as the component responsible for the clinical effects of the fumaric

acid esters.(73) DMF is predominantly hydrolysed to monomethyl fumarate (MMF) in the small intestine after it is oral intake.(74)

Fumaric acid esters have been shown to induce T-helper 2 cytokines, induce activated T-cell apoptosis, and down-regulate intracellular adhesion molecules (ICAM) and VCAM in the CNS.(45) These mechanisms are thought to influence the pathogenesis of MS via impaired cellular proliferation and migration across endothelial barriers.(45) DMF and metabolite MMF downregulate vascular cell adhesion molecule-1 expression in brain endothelial cells, resulting in reduced adhesion to activated endothelium and reduced transmigration across the BBB.(43)

Although, in human studies, results of the pregnancy outcomes when exposed to DMF early in pregnancy did not indicate increased foetal abnormalities, in rats tested at the highest dose showed increased lethalness, delayed ossification and sexual maturity, lower birth and testicular weight.(72) No formal studies of DMF have been conducted in pregnant women, although pregnancies have occurred during clinical trials and in the post-marketing setting, with this limited data and all the known exposures having occurred in the first trimester, no increased risk of foetal abnormalities or adverse pregnancy outcomes were associated with gestational exposure to DMF.(75) DMF should not be used during pregnancy or in patients of reproductive age who are not utilizing effective contraception.(76) DMF has a short half-life (of approximately 1h), hence a washout period is not required.(77) At this time, not enough research is carried out about dimethyl fumarate excretion in breast milk, so breastfeeding should be avoided.(72)

4.6 Cladribine

In June 2017 the European Medicines Agency granted marketing approval of cladribine tablets for multiple sclerosis, which became the first oral short-course treatment for highly active relapsing multiple sclerosis.(78)

Cladribine is a purine analogue, prodrug that reaches cells via nucleoside transporter proteins then it’s activated upon phosphorylation to its 2-chlorodeoxyadenosine triphosphate metabolite by the enzyme deoxycytidine kinase and de-phosphorylation occurs due to 5′-nucleotidase.(79)

The phosphorylated occurs specifically in lymphocytes due to their unique constitutively high deoxycytidine kinase levels and low 5′-nucleotidase levels

compared with other cells in the body.(79) Following activation of the cladribine in lymphocytes, 2-chlorodeoxyadenosine triphosphate may be incorporated into the DNA strands resulting in breaks and interference with DNA synthesis, leading to selective apoptosis.(79) B and T lymphocytes contain a higher deoxycytidine kinase to 5′-nucleotidase activity ratio than other cells types, in which 5′-nucleotidases balance the activity of deoxycytidine kinase and prevent 2-chlorodeoxyadenosine triphosphate accumulation.(79,80) As is Cladribine's mode of action, there is a selective reduction of the lymphocyte count which may lead to lymphopenia, moreover there might be an increase in the incidence of infections or malignancies associated with lymphopenia associated immunosuppression and reduction of cell-mediated immunity.(80)

Cladribine follows a limited cycle dosing schedule, administered in two yearly treatment courses in which each course consists of two treatment cycles, one cycle at the beginning of the first month and the other at the beginning of the second month.(81) Each treatment cycle lasts 4 or 5 consecutive days, depending on the patient's weight.(81) No cladribine treatment is required in the following two years after completing the 2 treatment courses.(82)

Cladribine tablets might cause congenital malformations when administered during pregnancy, based on human experience with other substances inhibiting DNA synthesis.(83) In mice and rabbits cladribine was found to be teratogenic when administered intravenously.(79)

Cladribine is contraindicated during pregnancy.(82,84) During cladribine treatment and for at least 6 months after the last dose, patients of childbearing potential must use effective contraception to avoid pregnancy.(82) The terminal half-life (tIS) of cladribine is about 7 to 19 hours.(85) According to experts taking into account its short tIS, a period of 6 months may be unnecessary long.(86) As the disease control of cladribine continues for at least 2 more years pregnancy planning can begin 6 months after completing the final dose in the second year of treatment.(87)

There is no indication for the termination of an unplanned pregnancy within 6 months after the last dose of cladribine, however, any further administrations of cladribine tablets should be discontinued immediately or delayed in this event.(81,83,88)

4.7 Sphingosine 1-Phosphate Receptor Modulators

Sphingosine 1-phosphate (S1P) is a soluble signalling molecule that interacts with the sphingosine 1-phosphate receptor (S1PR), a G protein-coupled receptor, to affect immunological, cardiovascular, and neurological processes.(89)

S1P is produced intracellularly by two sphingosine kinases (SphK1 and SphK2).(90) The S1PR has 5 subtypes: S1PR1, S1PR2, S1PR3, S1PR4, and S1PR5.(90) S1PR1, S1PR2, S1PR3, and S1PR5 are found in the CNS, expressed on neurons, astrocytes, oligodendrocytes, and microglia.(89) B- and T-lymphocytes predominantly express S1P1, in lymph nodes where S1P concentration is typically low, lymphocytes upregulate their S1P receptor expression.(90) When S1P agonistically interacts with its receptor, the bound product is internalized, causing activation and transient retention of the T cell.(90) Modulators of the S1P receptor act as indirect antagonists to the receptor's function and sequester lymphocytes in lymph nodes.(91)

4.7.1 Fingolimod

Fingolimod is a disease-modifying treatment for RRMS, which is approved as either first- or second-line therapy, depending on the country.(92) Fingolimod is a modulator of the S1PR that decreases circulating lymphocytes through sequestration in the lymph node.(45)

Once fingolimod is administered, sphingosine kinase type 2 phosphorylates fingolimod to fingolimod phosphate (fingolimod-P), the active metabolite that acts as an agonist at the S1P receptor.(90)

Fingolimod should not be taken during pregnancy as, during the critical time of embryogenesis, it has an effect on the receptors responsible for vascular system formation.(72) EMA currently has recommended the contraindication of fingolimod during pregnancy and in women of childbearing potential not using effective contraception, moreover if a patient becomes pregnant while taking fingolimod the medicine must be stopped and the pregnancy must be closely monitored, with organ screening ultrasound.(93) Fingolimod has been associated to foetal malformations, death, growth retardation, and cognitive deficits in rabbit and rat models.(28)

Patients able to have children must have a pregnancy test before initiating therapy with fingolimod to ensure they are not pregnant as well as use effective contraception during

treatment and for two months after stopping the medicine, the wash out period.(72,93) Furthermore it is required, a complete blood count, alanine aminotransferase ; aspartate transaminase, and varicella zoster immunoglobulin (Ig)-G titer examination (confirming exposure to chickenpox or shingles), before starting treatment.(90)

4.7.2 Siponimod

Siponimod is a receptor modulator that binds selectively to S1PR1 and S1PR5, and works by internalizing S1P1 receptors to reduce efflux of lymphocytes from the lymph nodes and thymus.(19,91) Siponimod is used to treat adults with secondary progressive MS.(94)

Animal studies have shown that siponimod and its metabolites are transferred to the foetus through the placenta.(24) In animal studies, siponimod revealed reproductive toxicity, in rats and rabbits including embryo-foetal deaths and skeletal or visceral malformations, at levels comparable to human exposure at a daily dose of 2 mg.(95) There are currently no clinical studies on the use of siponimod during pregnancy or nursing.(24) Siponimod is contraindicated during pregnancy and in patients of childbearing ability who are not using effective contraception due to the potential risk to the foetus.(95) Patients of childbearing potential must be informed of the risk to the foetus before starting treatment, have a negative pregnancy test, and use effective contraception during treatment and for at least 10 days after treatment discontinuation.(95) Siponimod must be stopped immediately if a patient becomes pregnant while on this medication.(95)

Siponimod goes through two stages of biotransformation, the first phase involves hydroxylation, which is primarily carried out by cytochrome P4502C9 (CYP2C9), and the second phase involves sulfation and glucuronidation.(96) Prior to starting Siponimod, patients must have CYP2C9 genetic testing to determine the proper dosing and titration schedule.(19)

4.7.3 Ozanimod

Ozanimod is an oral immunomodulatory drug used for the treatment of CIS, relapsing–remitting, and secondary progressive forms of MS.(19) Ozanimod modifies the course of disease by altering the activity of S1P1 and S1P5 receptors.(19) In addition to reducing the concentration of circulating autoreactive lymphocytes in the bloodstream, it prevents them from entering the CNS from peripheral tissues.(19)

Animal studies have revealed reproductive toxicity, including foetal loss and anomalies, such as blood vessel malformations, generalised oedema (anasarca), and mispositioned testes and vertebrae.(50)

Ozanimod is contraindicated during pregnancy and in patients of childbearing potential who are not using effective contraception due to the risk to the foetus.(50) Patients of childbearing potential must be informed about the risk to the foetus before starting treatment, have a negative pregnancy test, and use effective contraception during treatment and for 3 months after treatment has ended.(50) Resulting in the need for ozanimod to be stopped 3 months before attempting to conceive.(50) As well as it must be discontinued if a woman becomes pregnant while on Ozanimod.(50)

Ozanimod and metabolites were present in rat milk, therefore due to the risk of serious adverse reactions to ozanimod/metabolites in nursing infants patients taking ozanimod should not breastfeed.(50)

4.8 Monoclonal Antibodies

Monoclonal antibodies for the treatment of MS include natalizumab, ocrelizumab, ofatumumab and alemtuzumab.(51)

4.8.1 Natalizumab

Natalizumab is a monoclonal antibody directed against α4-integrin of VLA-4, preventing its binding to VCAM-1, which prevents lymphocyte migration across the BBB hence decreases inflammation.(45) It is indicated for the treatment of active RRMS as well as Crohn's disease.(97) α4 integrins are also active during embryonic development and genetic disruption of the α4 chain can have lethal consequences during embryogenesis.(98)

The Tysbari Pregnancy Exposure Registry was a global, observational, exposure registration and follow-up study to evaluate pregnancy outcomes of women who were exposed to natalizumab at any time within 3 months prior to conception or during pregnancy. The outcomes of 350 pregnancies exposed to natalizumab revealed no specific pattern of malformations that would suggest a drug effect, and the spontaneous abortion rate was comparable to the general population.(99)

Natalizumab does not cross the placenta during the first trimester, but it is actively transported during the second and third trimesters.(2) It is a possibility for patients with

high activity disease planning a pregnancy, moreover it can be used up to 30 weeks' gestation.(88) Experts recommend administering the last dose during pregnancy at approximately 34 weeks and restarting shortly after birth to reduce foetal exposure; within 8-12 weeks after the last dose, wherever possible, to prevent disease rebound activity.(2) If a patient with highly active RRMS wishes to become pregnant, the risks of natalizumab exposure during pregnancy must be weighed against the risks of disease activity returning following natalizumab withdrawal.(100) Late pregnancy exposure has been linked to minor, self-limiting haematological abnormalities in children.(2)

4.8.2 Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody that reduces T and B-lymphocytes, monocytes, and eosinophils via targeting CD52.(45)

Animal studies have reported increased embryo lethality and reduced levels of B and T lymphocytes in offspring when during the period of organogenesis pregnant mice were exposed to alemtuzumab.(72)

In a study reporting pregnancy outcomes in alemtuzumab-treated women from the phase 2 and 3 clinical development program reported a prevalence rate of major birth defects less than the global prevalence as well as the rate of spontaneous abortion in the clinical development program was comparable to that of the general population.(101) Alemtuzumab should only be administered during pregnancy if the potential benefit justifies the potential risk to the foetus.(102) Before each alemtuzumab cycle a negative pregnancy testing is required.(58)

Unlike DMTs that require more frequent administration, alemtuzumab's prolonged clinical effect without continuous dosing minimizes the risk of disease activity while avoiding foetal drug exposure.(101)

While it is not possible to calculate Alemtuzumab concentration in the plasma 1 month after the last dose, individuals with multiple sclerosis that are biologically able to get pregnant are advised to follow a 4 month wash out period, meaning to not to conceive for at least 4 months after alemtuzumab discontinuation.(72) Alemtuzumab has a half-life of 4-5 days hence its complete elimination after 30 days, so this 4-month window has no pharmacological justification.(58)

The possible development of secondary autoimmune diseases must be considered in pregnant women or those who plan a pregnancy.(58) Uncontrolled autoimmune thyroid

diseases, a common side effect of alemtuzumab, might increase the risk for miscarriages intrauterine growth retardation, preeclampsia and preterm birth (hyperthyroidism) or irregular menstruation, infertility and a restricted mental development of the child (hypothyroidism).(58) Patients previously treated with Alemtuzumab should have their thyroid function during pregnancy frequently tested as to avoid autoimmune thyroid disease for the patient and possible harmful effects to the foetus as the risk of autoimmune thyroid disease remains increased for 4 years after completing alemtuzumab treatment.(58,72) This is particularly critical in pregnancy, as antibodies against thyroid stimulating hormone receptors cross the placenta and may induce transient neonatal Graves disease.(72)

Breastfeeding is also not advised during treatment or within 4 months after receiving the last dose, even though data is not available from human studies, in animal studies alemtuzumab was detectable in the milk and offspring of lactating female mice.(58,72) It is likely that alemtuzumab can cross into the breastmilk, as other monoclonal antibodies.(58)

4.8.3 Ofatumumab

Ofatumumab is an immunoglobulin G1 (IgG1) kappa human monoclonal antibody with a molecular weight of ~149 kDa.(51) It is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis.(103)

Ofatumumab specifically binds to CD20 on the surface of B-cells, thus, it activates antibody-dependent cell-mediated cytotoxicity and complement-dependent cell lysis of CD20 overexpressing B-cells.(51) Ofatumumab has the advantage that it can be administered subcutaneously to be delivered subcutaneously by patients or caretakers using an auto-injector pen at four-week intervals, allowing for greater access to therapy than traditional antibody treatments.(104)

The information on the use of ofatumumab in pregnant patients is minimal.(105)

Use of ofatumumab during pregnancy and lactation may increase the risk of B-cell depletion in utero, transient peripheral B-cell depletion and lymphocytopenia in infants after birth and, hence, increase infections in the off-spring or unknown safety and efficacy profile of vaccinations in the new-born.(103) As a result, women of reproductive potential should use effective contraception while administering ofatumumab and for 6 months after the last administration.(103,105) Treatment with

ofatumumab during pregnancy should be avoided unless the potential benefit to the patient outweighs the potential risk to the foetus.(103,105)

Ofatumumab is classified in the pregnancy category risk C by the FDA.(106)

4.8.4 Ocrelizumab

Anti-CD20 monoclonal antibody therapy includes humanized ocrelizumab and chimeric rituximab.(72) As the evidence of ocrelizumab safety during pregnancy is insufficient, the greatest experience of anti-CD20 antibody treatment in MS comes from chimeric rituximab.(72)

Ocrelizumab has been approved for the treatment of active relapsing and primary progressive forms of Multiple Sclerosis.(104) Ocrelizumab has a Molecular Weight of approximately 145 kDa and is able to cross the placenta after the first trimester.(24) The half-life of Ocrelizumab is of 26 days.(24)

In animal studies done in primates administration of ocrelizumab during foetal organogenesis did not result in embryocytotoxic or teratogenic effects and had no effect on abortion or embryo-foetal fatality rate.(24) However, ocrelizumab in both the mother and the offspring was associated with peripheral B-cell depletion and immunosuppression with reconstitution of B-cells at 6 months of age.(24)

Data from 267 pregnancies in women treated with ocrelizumab did not indicate an increased risk of adverse events.(24) However, patients of childbearing potential should use effective contraception for at least 6 months (FDA recommendation) to 12 months (EMA recommendation) after the last ocrelizumab infusion.(24) Ocrelizumab should be avoided during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus.(24)

If Ocrelizumab infusions were to be administered during pregnancy, the B-cell count of the neonate should be tested in the newborn's umbilical cord blood and vaccination should be scheduled accordingly.(24,107) Newborns without B-cells should not be vaccinated until reconstitution of B-cells has occurred (normally after 6-10 months).(24)

4.8.5 Rituximab

Rituximab has not been approved by either the EMA nor the FDA for the treatment of MS, but rituximab is increasingly used due to the limited treatment options available, in particular in aggressive types of MS or neuromyelitis optica.(58)

Rituximab, the monoclonal IgG1 chimeric antibody targets the CD20 protein selectively, which is expressed on the surface of most B-cell lymphocytes.(58)

Animal studies with the administration of rituximab to pregnant cynomolgus monkeys during organogenesis showed peripheral B-cell depletion and immunosuppression in the offspring, with B-cell reconstitution occuring usually by 6 months of age, although no teratogenic consequences were seen.(58,72) A study was done analysing 90 live birth outcomes of women inadvertently conceiving during or less than 12 months after the treatment of rituximab, which reported 22 premature births, one neonatal death after 6 weeks, 11 new-borns with haematological changes (B-cell deficiency, neutropenia, thrombocytopenia, anaemia, lymphopenia), four new-born's infections and two inborn malformations, a rate consistent with what is seen in the general obstetric population.(72,108) There was no pattern of congenital anomalies found to be associated to rituximab exposure.(108) Although there does not appear to be a pattern of teratogenicity or embryotoxicity, the limited cohort size cannot be interpreted to mean that rituximab use in the preconception period is safe.(108)

Rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk to the foetus.(109)

It is recommended a 12 month washout period after rituximab exposure, in which patients of childbearing potential should use effective contraceptive methods.(109,110) Although some authors do not recommend such a long washout, as it may increase the risk of return of MS disease activity in the postpartum year.(111,112) If a patient conceives accidentally before rituximab elimination, the risk of foetal exposure is low since IgG1 subclass antibodies are not transferred through the placenta during the first trimester.(113)

Given the depletion of B-cells by rituximab, health care providers should be aware of the possibility of immunosuppression and the resulting risk of neonatal infections.(58) The neonate B cell count should be tested before vaccinations following Rituximab infusions during pregnancy.(58)

To avoid potential harm to the new-born, rituximab should be avoided when breastfeeding and the patients should be advised not to breastfeed 6 months after discontinuing the treatment, as in animal studies rituximab was detected in lactating cynomolgus monkey's milk.(58,72)

Table 1. Recommendations for disease-modifying therapy use in pregnancy.

DMT	Pre-pregnancy washout	Pregnancy use	Recommendation for the use of DMT
Beta-interferon	Not necessary	Probably acceptable based on a large amount of data from interferon beta registries, national registries, and post-marketing experience	May be continued until positive pregnancy test, or if more active continued during pregnancy No harmful effects on the breastfed new born/infant are anticipated
Glatiramer acetate	Not necessary	Probably acceptable	May be continued until positive pregnancy test, or if more active continued during pregnancy
Mitoxantrone	4 months	Not used	Before each dose, a pregnancy test should be conducted. Contraindicated without effective contraception and during pregnancy
Teriflunomide	Accelerated elimination procedure (until blood level < 0.02 µg/ml)-8-24 months	Not used	Negative pregnancy test and contraception required for use in patients with childbearing potential Contraindicated without effective contraception and during pregnancy
Dimethyl fumarate	Probably not necessary	Not used	Negative pregnancy test and contraception required for use in patients with childbearing potential
Cladribine	6 months	Not used	Contraindicated without effective contraception and during pregnancy. Discontinue any further treatment until after pregnancy.
Fingolimod	2 months	Not used	If accidental pregnancy exposure occurs: stop fingolimod and must be closely monitored Contraindicated without effective contraception and during pregnancy
Siponimod	10 days	Not used	Contraindicated without effective contraception and during pregnancy, In unplanned pregnancy discontinue siponimod immediately
Ozanimod	3 months	Not used	Contraindicated without effective contraception and during pregnancy, In unplanned pregnancy discontinue ozanimod immediately
Natalizumab	Probably not necessary	Can be considered	May be continued until positive pregnancy test, or if highly active continued during pregnancy (every 8 weeks and last dose ~34 weeks), evaluate neonate for haematological abnormalities
Alemtuzumab	4 months	Not used	Negative pregnancy test required before each course.Maintain effective contraception for at least 4 months after last infusion.
Ofatumumab	6 months	Not used	Maintain effective contraception for at least 6 months after the last course. Discontinue any further treatment until after pregnancy
Ocrelizumab	According to EMA 12 months after the last infusion According to FDA 6 months after the last infusion	Not used	Maintain effective contraception for at least 6 months after the last course. Discontinue any further treatment until after pregnancy.
Rituximab	12 months	Not used	Maintain effective contraception for at least 12 months after the last course. Discontinue any further treatment until after pregnancy.

5 Symptomatic Treatments

Pharmacological therapy is an important part of managing MS symptoms, and a patient-centred approach is critical to its success.(114)

5.1 Spasticity

Spasms are sudden, involuntary, often painful movements affecting any part of the body.(115) Spasticity affects around 90% of MS patients at some point in their lives, it is often a disabling symptom caused by axonal degeneration or dysfunction, which may be paired with demyelinating plaques within specific descending spinal tracts.(116) Demyelinating plaques disrupt inhibitory interneuronal spinal network pathways, resulting in physiological flexor muscle weakness, frequently accompanied by increased (‘spastic') muscular tone and decreased dexterity of the muscles involved.(116) Spasticity can be divided into two category: tonic (permanently elevated muscle tone) and phasic (intermittently elevated muscle tone), often associated with painful cramps.(116)

5.1.1 Baclofen

Baclofen is a gamma-aminobutyric acid (GABA) inhibitory neurotransmitter analogue that inhibits spinal mono- and polysynaptic reflexes by binding GABA B receptors presynaptically in the Ia sensory afferent neurons, interneurons, and postsynaptically in the motor neurons reducing activity.(117,118) Calcium influx is reduced, excitatory neurotransmitter release is suppressed, and potassium conductance increases postsynaptically.(117) It is the most common muscle relaxant and antispasmodic used for the relief of spasticity in MS patients.(117) Baclofen is a first-line drug to treat spasticity in MS.(115)

Baclofen has been observed to increase the incidence of omphaloceles (ventral hernias) in rat foetuses when administered approximately 13 times the maximum dose recommended for human use, at a level that induced significant reductions in food intake and weight gain in dams.(119) This defect was not observed in mice or rabbits.(119) There was also an increased incidence of incomplete sternebral ossification in foetuses of rats given approximately 13 times the maximum recommended human dose, and an increased incidence of unossified phalangeal nuclei of forelimbs and hindlimbs in foetuses of rabbits given approximately 7 times the

maximum recommended human dose.(119) Teratogenic effects were not found in mice, however when giving dams 17 or 34 times the human daily dosage, resulted in decreases in mean foetal weight and delays in skeletal ossification.(119)

Baclofen should only be used during pregnancy if the possible benefit outweighs the risk to the foetus.(120)

Evidence from the limited literature suggests that the use of intrathecal baclofen therapy delivered via an implantable pump or catheter is not contraindicated in pregnancy and may in fact be a safer option than oral agents for the treatment of spasticity in pregnancy.(119)

5.1.2 Gabapentin

Gabapentin is a ligand of the alpha-2δ1 subunit of voltage-dependent calcium channels and it inhibits calcium currents.(121) Gabapentin reduces the impairment of spasticity in MS as measured by both physician-administered and subject self-report scale.(122) It is considered a first-line drug to treat spasticity in MS.(115)

A study comparing the outcomes of 223 pregnancies exposed to gabapentin to 223 unexposed pregnancies showed that the rates of major malformations were similar in both groups.(123) As well as none of the 36 women exposed only to gabapentin with no concomitant medications delivered a baby with a major malformation.(123)

A study with 1,753,865 pregnancies, with 4,642 (0.26%) exposed to gabapentin during the first trimester, 3,745 (0.21%) exposed to gabapentin early in pregnancy only (during the first 140 days), 556 (0.03%) exposed late in pregnancy but not early, and 1,275 (0.07%) exposed in both early and late pregnancy, did not find evidence for an association between gabapentin exposure during early pregnancy and major malformations overall however there was some evidence of a higher risk of cardiac malformations.(124) The prevalence of overall major congenital and cardiac malformations was 5.0 and 1.9 per 100 live births, respectively, among pregnancies exposed to gabapentin during the first trimester, and 3.3 and 1.1 per 100 among unexposed pregnancies.(124)

Gabapentin should only be used during pregnancy if the benefits to the mother clearly outweigh the risks to the foetus.(125)

Pregnant women using gabapentin during pregnancy may be considered for targeted interventions to monitor for and promptly respond to the potential adverse outcomes associated with the use of this agent. (124)

5.1.3 Tizanidine

Tizanidine is a short-acting muscle relaxant that inhibits the release of excitatory neurotransmitters at the spinal and supraspinal levels by stimulating central alpha2-adrenergic receptors.(118)

Tizanidine is classified as a category C pregnancy drug by the FDA.(126)

Reproduction studies in rats at a dose equivalent to the maximum recommended human dose in mg/m^2 and in rabbits at a dose 16 times the maximum recommended human dose in mg/m^2 revealed no evidence of teratogenicity.(126) However tizanidine at mg/m2 levels equivalent to and up to 8 times the maximum recommended human dose extended gestation duration in rats.(126)

There are have been no controlled studies in pregnant patients, therefore it should only be given during pregnancy after careful consideration between the risks for the unborn and gain for the mother.(126,127)

5.1.4 Dantrolene

Dantrolene is a second-line treatment for spasticity in MS patients.(115)

The mechanism of action of dantrolene decreases the release of calcium, acting on the contractile mechanism of skeletal muscle. However, due to the high frequency of side effects, such as gastrointestinal symptoms, weakness, fatigue, sedation, and dizziness, the use of dantrolene is limited.(118) Specifically hepatotoxicity which is the most important side effect, as such liver function must be monitored carefully.(128)

When given at doses seven times the human oral dose, dantrolene has been shown to be embryocidal in rabbits and to reduce pup survival in rats.(129) In pregnant women, there are no adequate and well-controlled studies.(129) Only if the potential benefit outweighs the risk to the foetus should dantrolene be taken during pregnancy.(130)

5.1.5 Benzodiazepines

In patients with MS, benzodiazepines are administered as a third line treatment for spasticity.(115)

Diazepam belongs to the benzodiazepine family of drugs.(57) Diazepam contributes to muscular relaxation by enhancing the action of the neurotransmitter GABA and suppressing neuronal activity in the reticular formation.(118) Diazepam is used to treat muscle spasms and spasticity in people with multiple sclerosis.(131)

An increased risk of congenital malformations and other developmental abnormalities associated with the use of benzodiazepine drugs during pregnancy has been suggested, also non-teratogenic risks associated with the use of benzodiazepines during pregnancy.(132) Diazepam is classified as a pregnancy category D drug by the Food and Drug Administration.(133) Due to their high lipid solubility, diazepam and its major metabolite, N-desmethyldiazepam, which are both pharmacologically active, freely cross the human placenta during early pregnancy.(117) Children born to mothers who took benzodiazepines late in pregnancy have been reported to have neonatal flaccidity, respiratory and feeding difficulties, and hypothermia.(132) Furthermore, children born to mothers who take benzodiazepines on a regular basis late in pregnancy may experience withdrawal symptoms in the postnatal period.(132) Prenatal diazepam exposure in rodent studies at doses comparable to those used clinically has been shown to cause long-term changes in cellular immune responses, brain neurochemistry, and behaviour.(132)

In general, diazepam should only be used in women of reproductive potential, and particularly during known pregnancy, when the clinical circumstance warrants the risk to the foetus.(117,132)

Clonazepam is a long-acting benzodiazepine that lowers monosynaptic and polysynaptic reflexes while increasing presynaptic GABA inhibition.(134) By facilitating inhibitory GABA neurotransmission and other inhibitory transmitters, it reduces muscular contractions.(134) A study using surveys sent to participants who indicated mild or greater tremor using the Tremor and Coordination Scale found that among users of benzodiazepines, clonazepam was the most commonly reported beneficial drug.(135)

Clonazepam is a Pregnancy Category ‘D’ drug according to the FDA.(136)

A pattern of malformations (cleft palate, open eyelid, fused sternebrae, and limb defects) was observed in studies where a low dose of about 0.2 times the maximum recommended human dose was given orally to pregnant rabbits during the period of

organogenesis.(137) In mice and rats, no adverse maternal or embryo-foetal effects were observed after oral doses up to 4 and 20 times the maximum recommended human dose for seizure disorders and 20 and 100 times the maximum dose for panic disorder were administration during organogenesis.(137) In a study, 43 clonazepam monotherapy new-borns were identified, 33 of whom were exposed during the first trimester and one of whom had a major malformation. As a result of the findings of this study, there was no increase in major malformation. However, the sample size of this study is insufficient to determine whether the rate of major malformations is higher in clonazepam-exposed pregnancies.(138)

Clonazepam should only be used in individuals of reproductive potential, and specifically during known pregnancy, when the clinical situation clearly indicates a benefit to the mother when compared to risk to the foetus.(136)

5.2 Walking impairment

Fatigue, difficulties walking, stiffness and spasms, memory and other cognitive problems, bladder difficulties, pain and other unpleasant sensations, emotional or mood difficulties, eyesight problems, dizziness or vertigo, and bowel difficulties were the top 10 symptoms reported by MS patients.(139) The lower extremities are the most commonly affected by motor deficits in MS patients.(140)

Walking impairment causes a slowing of gait as well as a loss of endurance, limiting one's ability to engage in community activities such as home activities, social activities, and work.(141) Thus one of the most common and impactful effects of MS is mobility disability.(142) As a result, improving walking in MS patients is critical.(141)

5.2.1 Fampridine

Fampridine is a sustained-release matrix tablet of 4-aminopyridine (4-AP), a K+ channel blocker.(142) It is a broad-spectrum lipophilic potassium channel blocker that binds preferentially to the open state of the potassium channel in the CNS.(143) Its pharmacological targets are the potassium channels exposed in MS patients; prolonging repolarization and thus enhancing action potential formation in demyelinated axons and neurological function.(143,144) More impulses might be conducted in the central nervous system if action potential formation is improved.(144) 4-AP also increases calcium (Ca^{2+}) influx at presynaptic terminals, thereby enhancing neuro-neuronal or neuromuscular transmission in normally myelinated neurons.(143)

Studies in animals have found decreased offspring survival and growth when doses comparable to a human dose of 20 mg/d were administered during pregnancy and lactation.(145) Extended-release fampridine's safety in pregnancy and breast-feeding is unknown at the moment, so it should probably be avoided in these circumstances.(146) Only one pregnancy exposure with a normal delivery at week 40 after 25 days of exposure has been published.(147) As such fampridine should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.(148)

5.3 Fatigue

Fatigue is defined as a feeling of exhaustion or a lack of energy that is greater than one would expect given the daily effort and degree of disability.(149) Typically fatigue is characterised as a desire to rest that is often accompanied by a loss of motivation and patience, and it is exacerbated by exercise, the end of the day, and depression.(150) Although it shares certain characteristics with fatigue experienced by healthy adults, it is more severe and has a more disabling effect on daily activities.(150)

Amantadine and modafinil are the primary medications used to treat fatigue in MS patients.(151)

5.3.1 Amantadine

Amantadine is approved by the FDA for treatment of influenza, and as it also has anti parkinsonism properties it is FDA-approved for Parkinson disease.(152)

The mechanism of action is thought to involve blocking presynaptic dopamine reuptake and stimulating postsynaptic receptors.(151)

Amantadine is the only oral treatment for MS-related fatigue that the National Institute for Health and Care Excellence (NICE) currently recommends.(115)

Amantadine exposure during the first trimester is demonstrated to be embryotoxic and teratogenic in rats receiving 12 times the recommended human dose, causing cardiovascular malformations.(153,154) Amantadine treatment during pregnancy has been reported in four cases, all of which have resulted in complications, including two miscarriages.(147) Amantadine should be avoided during pregnancy, according to the evidence summary.(155)

5.3.2 Modafinil

Modafinil is a drug currently approved for the treatment of attention-deficit hyperactivity disorder (ADHD) and narcolepsy.(156)

The consensus group of neurologists selected modafinil as a first-line drug for treating MS-related fatigue; and it is indicated for the treatment of severe fatigue.(151)

Animal reproductive toxicity studies conducted in rats and rabbits have showed an increased incidence in skeletal variations (changes in the numbers of ribs and delayed ossification), embryo-foetal lethality (peri implantation loss and resorptions) and some evidence of an increase in stillbirths (rats only), in the absence of maternal toxicity, at clinically relevant exposures.(157) At systemic exposures equivalent to the maximum recommended human dose, there was no effect on fertility and no evidence of teratogenic potential.(157) Toxicity studies on reproduction found no effect on fertility, no teratogenic effect, and no effect on offspring viability, growth, or development.(157) In general toxicology, reproductive, and carcinogenicity studies, animal exposure to modafinil on a mg/kg dose basis was higher than expected human exposure calculated on a similar basis.(157)

Based on limited human experience from a pregnancy registry and spontaneous reporting modafinil is suspected to cause congenital malformations when administered during pregnancy.(158) Even though further research is needed, patients contemplating pregnancy should currently avoid or discontinue modafinil.(159)

Women of childbearing potential have to use effective contraception during treatment with, and for 2 months after stopping, modafinil.(157,160) Seeing as modafinil may reduce the effectiveness of oral contraception, additional or concomitant methods of contraception methods are required.(158,160)

6 Practical Guidance for Pregnancy in Multiple Sclerosis Patients

In people that suffer from a chronic disease who are biologically capable of becoming pregnant pregnancies should be planned if possible and the best treatment strategy discussed beforehand.(58) At or soon after diagnosis, all women with MS of child-bearing age should have pre-pregnancy counselling in addition to having these consultations repeated at regular intervals (at least annually) particularly for those who are on or considering starting medication.(2) When planning a pregnancy, important counselling and management considerations for patients include both effects of pregnancy on MS and effects of MS on fertility, genetic counselling, and preconception care including discontinuation of MS therapies.(32) The possible necessity for instrumental delivery should be taken into account when planning the delivery of a patient with MS.(30) The decision to become pregnant in a patient with MS should be considered at a time when disease activity is low.(161)

Women with MS should be advised to follow standard advice for all pregnant women, such as smoking cessation, alcohol abstinence, termination of stimulant use, following a balanced diet rich in omega-3 polyunsaturated fatty acids, and the intake of folic acid.(2,40,41) In addition to habitually recommended prenatal vitamins and 0.4–1.0 g daily of folic acid, MS-specific preconception considerations include emphasis on smoking cessation as a result of a possible role in disease progression, performing pelvic floor exercises, sleep hygiene counselling, and vitamin D supplementation.(2,32)

Magnetic resonance imaging is not contraindicated at any time during pregnancy however should only be considered if it is absolutely indicated with the findings having therapeutic consequences, when possible MRI with gadolinium contrast media should be avoided.(24)

The general criteria for a safe pregnancy in patients with MS is the remission period, the washout period specific for each DMT, favourable prognosis of the disease, folic acid intake in a prophylactic dose for at least three months before a planned pregnancy, and vitamin D supplementation in the case of deficiency, as well as for individual cases the consideration of pregnancy during administration of some DMTs.(40)

DMTs should be started or maintained in all patients with Relapsing-remitting MS with recent activity regardless of the desire to become pregnant.(161) Child- bearing aged patients should not defer disease- modifying drug treatment because they wish to have children in the future.(2)

Due to the decrease in relapses that typically occurs during pregnancy, most women are able to safely discontinue treatment for pregnancy.(35) There are many reports of patients with MS having improved symptoms during pregnancy, however pregnancy can have impact specific functional abilities such as cardiovascular conditioning, spasticity, and mood.(112) As a general practice in the clinical setting patients should be monitored and have when warranted multidisciplinary referrals (e.g., psychologist, psychiatrist, physical therapist, pelvic floor therapist, and/or urologist).(112)

Patients with more active MS or on DMTs with risk of disease reactivation upon discontinuation should carefully plan treatment before pregnancy to decrease relapse risk.(35)

In a clinical setting DMTs can be separated into categories according to their potential pregnancy-associated risk and foetal outcome; the first group includes beta interferon, acetate of glatiramer and natalizumab, which can be continued until pregnancy is confirmed.(24)

Once a pregnancy has been confirmed, a decision must be made about whether to continue or discontinue treatment, taking into account the benefit to the mother and the potential risk to the foetus.(24) For pregnant women with severe or highly active MS, the benefit of MS treatment may outweigh the (unknown) risk to the foetus.(2) If such treatment is necessary, clinicians may consider switching to a different drug.(69) Even though evidence-based data supporting the use of DMTs in pregnancy remains limited, the evidence is stronger for the use of interferon- β compared to other DMTs.(27) The DMTs with most practical experience are IFN-β and GA, which are administered subcutaneously.(162) Limited available data indicates a low risk of foetal harm for glatiramer acetate, dimethyl fumarate, natalizumab, and alemtuzumab.(27)

Among DMTs, those who have been used during pregnancy are beta interferon and acetate of glatiramer, as there is extended information on its safety from post-marketing records.(161) Glatiramer acetate and interferon beta are the most routinely recommended modestly effective disease-modifying therapies for women who are

planning a pregnancy within the next 2 years or not on reliable birth control.(111,161) Accidental first-trimester exposure with glatiramer acetate or interferon beta appears innocuous and both disease-modifying therapy types are easy to use in general practice settings, as interferon beta requires only limited additional safety monitoring and glatiramer acetate requires none.(111) If IFN-β or Glatiramer acetate are interrupted during pregnancy, it is expected to take several months for the DMT to be able to reach full efficacy after restarted thus not reducing the relapse rate during the first few months postpartum.(2) Current clinical opinion recommends that patients with multiple sclerosis should stop using disease-modifying medicines before getting pregnant; however, those with severe or highly active MS may consider continue taking glatiramer acetate or IFN-β during pregnancy.(69) In exceptional cases, in very active MS, the use of natalizumab can also be considered during pregnancy.(161)

The second category of the clinical classification refers to those DMTs that prior to attempting to conceive should be stopped, as well as effective contraception is highly recommended during the wash-out period; and includes teriflunomide, DMF, fingolimod, cladribine, siponimod, alemtuzumab, and ocrelizumab.(24) In case of unintended pregnancy, these DMTs should be immediately discontinued.(24)

After the birth the status of both the health of the mother and the child are crucial considerations regarding the resumption of DMT therapy.(27)

Treatment for relapses may not be necessary if relapse symptoms are mild and do not impair function.(8,163) Relapses during pregnancy can be treated with the standard short courses of high-dose steroids (intravenous methylprednisolone [500 mg-1000mg] for 3 to 5 days).(35,163) However caution is advised prior to gestational week 12 because of the risk of cleft palate.(29) In the case of severe relapse in the first trimester, the preferred treatment is prednisolone as it is inactivated in the placenta; only about 10% reaches the foetus versus 100% with dexamethasone.(29)

7 Discussion/Conclusion

Multiple sclerosis is most often diagnosed in young adults during their reproductive years with approximately a 3:1 female-to-male ratio. Hence the importance of patients being educated about reproductive issues relating to the management of Multiple Sclerosis during pregnancy.

For patients with MS who become pregnant, the risks and benefits of ongoing therapy for the health of both the mother and the foetus must be carefully assessed. As well as often new medications enter the market without data on their safety during pregnancy. Data on the efficacy and/or safety of MS therapies during pregnancy remain limited, however data registry studies are providing essential real-world data allowing healthcare professionals and patients to weigh the benefit of specific MS treatments against the potential risks to the foetus.

As some DMTs should not be used in pregnancy and in those attempting to conceive there is a need for effective and safe contraception. Most forms of contraception appear to be safe for MS patients based on current evidence.

The general recommendation continues to be the discontinuation of DMTs before conception except for individual cases with severely active MS. The decision to stop or continue using a particular drug during pregnancy or nursing must be carefully considered by both the treating physician and the patient. In addition, a patient taking a DMT with limited pregnancy safety evidence may be switched to a DMT with more safety data, such as an interferon beta or glatiramer acetate. And in the cases of very active MS use natalizumab.

MS symptoms can have an intense effect on quality of life of patients. Symptoms such as spasticity, walking impairment and fatigue can be debilitating and the pharmacological treatment is an important component its management. These treatments, on the other hand, should only be used during pregnancy if the potential benefit outweighs the risk to the foetus.

Patients with MS wishing to become pregnant should follow standard advice for all pregnant women with a special focus in smoking cessation, pelvic floor exercises, sleep counselling, acid folic intake for at least 3 months prior to conception and vitamin D supplementation. Pregnancy should be planned, and the conception should be

considered at a time when MS activity is low, and if DMT is needed following the washing period of the DMT the patient is taking.

During pregnancy MS relapses can be treated using steroids.

Further research into the efficacy of the current recommendations by the European Medicines Agency in the restriction of DMT use during pregnancy is required, as data quantifying the decrease in adverse pregnancy outcomes is currently unavailable.

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