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REVIEW ARTICLE

Fertility, Pregnancy and Childbirth in Patients with Multiple Sclerosis: Impact of Disease-Modifying Drugs

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Abstract In recent decades, pregnancy-related issues in multiple sclerosis (MS) have received growing interest. MS is more frequent in women than in men and typically starts during child-bearing age. An increasing number of disease-modifying drugs (DMDs) for the treatment of MS are becoming available. Gathering information on their influences on pregnancy-related issues is of crucial importance for the counselling of MS patients. As for the immunomodulatory drugs (interferons and glatiramer acetate), accumulating evidence points to the relative safety of pregnancy exposure in terms of maternal and foetal outcomes. In case of higher clinical disease activity before pregnancy, these drugs could be continued until conception. As for the 'newer' drugs (fingolimod, natalizumab, teriflunomide, dimethyl fumarate and alemtuzumab), the information is more limited. Whereas fingolimod and teriflunomide are likely associated with an increased risk of foetal malformations, the effects of natalizumab, dimethyl fumarate and alemtuzumab still need to be ascertained. This article provides a review of the available information on the use of DMDs during pregnancy, with a specific focus on fertility, foetal development, delivery and breast-feeding.

Key Points

Gathering information on the influences of available disease-modifying drugs on fertility, pregnancy and childbirth is of crucial importance for the counselling of patients with multiple sclerosis. To this end, the implementation of multicentre international pregnancy registries in the post-marketing phase is advocated.

There is mounting evidence of the relative safety of pregnancy exposure to interferons and glatiramer acetate in terms of maternal and foetal outcomes. In case of higher clinical disease activity before pregnancy, these drugs could be continued until conception.

Fingolimod and teriflunomide are likely associated with an increased risk of foetal malformations. For teriflunomide, an accelerated elimination procedure is available in case of unexpected pregnancy or pregnancy planning.

The effects of pregnancy exposure to natalizumab, dimethyl fumarate and alemtuzumab need further assessment.

All of the drugs should be avoided during lactation, since excretion in human milk has been demonstrated or is unknown, and a risk to the newborns cannot be excluded.

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1 Introduction

Multiple sclerosis (MS) is an autoimmune condition affecting the central nervous system (CNS). The pathological

hallmarks of MS are diffuse and focal areas of inflammation, demyelination, gliosis and neuronal injury in the brain and spinal cord. MS is the most common non-traumatic cause of neurological disability in persons younger than 40 years. It mainly affects young people, with onset usually at the age of 20–40 years, and it occurs in a female-to-male ratio of 3–1 [1, 2]. Although the clinical course of the disease is highly variable, 85–90 % of patients at disease onset have a relapsing–remitting MS (RRMS) course, characterized by clearly defined attacks of new or recurrent neurological symptoms and signs, followed by a full or partial recovery. In 10–15 % of the cases, the disease is characterized by a disability progression from onset, with occasional plateaus and temporary improvements (a primary progressive course). In natural history studies of untreated cohorts, approximately 50 % of RRMS patients after 10 years and 90 % after 25 years convert to secondary progressive MS (SPMS), characterized by disability progression with or without occasional relapses, minor remissions and plateaus [3–5].

Since 1993, an increasing number of medications have been developed, aimed at reducing the relapse rate, the accumulation of disability and the lesion burden on magnetic resonance imaging (MRI)—the so-called disease-modifying drugs (DMDs). To date, approved therapies for RRMS include interferon (IFN)-β, available in different formulations (for intramuscular or subcutaneous administration); glatiramer acetate (GA); natalizumab; fingolimod; mitoxantrone; and the newer agents teriflunomide, alemtuzumab and dimethyl fumarate. They can be broadly classified as first-line and second-line treatments; the latter are used in patients who do not respond satisfactorily to a first-line therapy or in patients with very active RRMS [6, 7].

1.1 First-Line Disease-Modifying Drugs

IFN-β was the first DMD approved for the treatment of RRMS and has for several years been the mainstay in MS therapy. Different formulations of IFN-β are available, differing in the route (intramuscular or subcutaneous injections) and frequency of administration (once weekly or several times weekly). Subcutaneous IFN-β1b every other day was approved in 1993, intramuscular IFN-β1a once weekly in 1996 and subcutaneous IFN-β1a three times weekly in 1998. In 2014, a pegylated version of intramuscular IFN-β1a, administered every 2 weeks, was approved (Table 1) [8–12].

The other first-line immunomodulatory agent for the treatment of RRMS is GA, a mixture of polypeptides composed of four amino acids. GA is administered subcutaneously in a dose of 20 mg daily. It was approved in 1996 (Table 1) [8, 13].

The safety of injectable first-line therapies is, in general, excellent. The most frequent side effects of IFN are injection site reactions, flu-like symptoms and the occurrence of neutralizing antibodies [9–11, 14, 15]. For GA, self-limiting feelings of chest tightness, dyspnoea and palpitations, together with injection site reactions, have been reported [13]. It has to be noted that the occurrence of haemolytic-uraemic syndrome has been recently reported in a few patients treated with IFN [16, 17].

Among the new agents approved as first-line therapy for RRMS, teriflunomide is a dihydroorotate dehydrogenase inhibitor, which causes inhibition of proliferation of autoreactive B and T cells and is administered orally in a dose of 14 mg once daily. It was approved in 2012 [18]. The effects on relapses, confirmed Expanded Disability Status Scale (EDSS) scores and MRI activity are substantially comparable to those of the injectable first-line therapies (Table 1) [19–21].

Dimethyl fumarate reduces the production and release of inflammatory molecules and has antioxidant properties [22]. It was approved in 2013 and is administered orally as a 240 mg tablet twice daily (Table 1) [23, 24]. The new first-line oral therapies appeared to be well tolerated in the phase III trials. For teriflunomide, common side effects include hair thinning and gastrointestinal symptoms; for dimethyl fumarate, common side effects include flushing and gastrointestinal symptoms [19, 24].

1.2 Second-Line Disease-Modifying Drugs

Natalizumab, mitoxantrone and alemtuzumab are approved as second-line therapy for patients with high disease activity despite treatment with first-line agents, or as first-line therapy in very active RRMS [7]. Fingolimod is approved as first-line therapy by the US Food and Drug Administration (FDA) and as second-line therapy by the European Medicines Agency (EMA). Mitoxantrone is also approved by the FDA for treatment of SPMS.

Natalizumab (approved in 2004) is a humanized monoclonal antibody, which inhibits lymphocyte migration across the blood–brain barrier (Table 1) [25, 26]. The major concern with natalizumab therapy is the development of progressive multifocal leukoencephalopathy (PML) [27]. Today, risk stratification is possible, as the presence of the John Cunningham virus (JCV) can be determined by measurement of anti-JCV antibodies in the blood [28, 29]. Moreover, mild lymphocytosis, hepatotoxicity and infusion reactions have been reported in a small proportion of patients [25, 26].

Fingolimod, a sphingosine-1-phosphate (S1P) analogue, causes a reduction of the circulating lymphocyte count in the peripheral blood [30]. It was approved in 2011 and is administered as a 0.5 mg capsule once daily (Table 1) [31,

Table 1 Efficacy of disease-modifying drugs versus placebo in pivotal trials in relapsing–remitting multiple sclerosis

Drug (generic name)	Year of first approval	Relapse rate reduction (%)	Confirmed EDSS disability reduction	MRI activity reduction (new lesions, Gd+ lesions) (%)
Interferon-β	1993–1998	~30	Inconsistent	~60–80
Glatiramer acetate	1996	~30	Inconsistent	~30
Mitoxantrone	2000	~60	~64 %	~85
Natalizumab	2004	~68	~42 %	~80–90
Fingolimod	2011	~50	~37 %	~75–80
Teriflunomide	2012	~30	Inconsistent	~70
Dimethyl fumarate	2013	~50	~38%	~80–90
Alemtuzumab[a]	2013	~40–50	~30 %	~70

EDSS Expanded Disability Status Scale, *Gd+* gadolinium-enhancing, *MRI* magnetic resonance imaging

[a] The data are versus interferon-β1a 44 μg three times weekly

32]. S1P receptors are expressed in many body tissues, explaining a number of unwarranted effects of fingolimod. After the first dose of fingolimod, bradycardia and atrioventricular conduction block have been reported in fewer than 2 % of patients [31–33]. Other side effects are macula oedema, elevated liver function tests, an increased risk of infections (fatal herpes virus in a few cases) and hypertension [31, 32].

Alemtuzumab (approved in 2013) is a humanized monoclonal antibody against CD52, which causes a long-lasting depletion of lymphocytes. Alemtuzumab is administered intravenously, 12 mg daily for 5 days and, after 12 months, 12 mg daily for 3 days (Table 1) [34–36]. Alemtuzumab frequently causes infusion-related side effects and mild-to-moderate infections. Immune-mediated hypothyroidism or hyperthyroidism occurs in 34 % of patients treated with alemtuzumab [34–36], whereas idiopathic thrombocytopenia has been detected in 2 % of patients, and a few patients have developed renal failure because of Goodpasture's syndrome [34–36].

Approved in 2000, mitoxantrone is a strong immunosuppressant administered in a dose of 12 mg/m^2 intravenously at 3-month intervals (Table 1) [37]. Mitoxantrone causes chemotherapy-induced reversible bone marrow suppression and nausea. Amenorrhoea has been reported in more than 20 % of fertile women [38, 39]. Dose-dependent cardiotoxicity has been observed, particularly above a cumulative dose of 120 mg/m^2. Therapy-related acute leukaemia has been detected in up to 1 % of patients [40, 41].

Although it has not received formal approval, another immunosuppressant agent widely used in MS is cyclophosphamide, an alkylating chemotherapeutic agent that binds to DNA and interferes with mitosis and cell replication [42]. In the past three decades, extensive experience with cyclophosphamide in patients with MS has been accumulated, showing an efficacy and safety profile comparable to that of mitoxantrone [42, 43]. The major safety issues include bladder cancer and gonadal toxicity. Common side effects reported in the clinical trials are alopecia, nausea/vomiting, transient myelosuppression, haemorrhagic cystitis, amenorrhea and transient azoospermia [42, 44].

2 Fertility, Pregnancy, Foetal Development, Delivery and Breast-Feeding in Multiple Sclerosis

Pregnancy-related issues have become more and more frequent in MS [45–47]. The disease is more prevalent in females than in males and typically starts during childbearing age. The female-to-male ratio has increased in recent decades [48–50], probably because of lifestyle changes (such as smoking, sunlight exposure and vitamin D deficiency) [51] and epigenetic factors and gene–environment interactions [52]. Moreover, the times to diagnosis and to treatment have been significantly shortened [53]. Therefore, providing information on the reciprocal influences between MS and pregnancy, and the impact of treatments, is of crucial importance for the management of MS patients in the everyday clinical setting (Table 2).

Sexual dysfunction is often under-reported by MS patients and has a negative impact on quality of life [54, 55]. Its prevalence ranges from 30 to 70 % of cases, depending on the clinical characteristics of study samples and on follow-up durations [56]. Women with MS most frequently report reduced libido (36–86 % of cases), difficulty in achieving orgasm (28–58 %), reduction in the tactile sensations from genital areas (43–62 %) and dyspareunia (8–40 %) [56–58]. Men most frequently report reduced libido (37–86 %), erectile dysfunction (34–80 %), reduction in tactile sensations (21–72 %), ejaculatory dysfunction (34–61 %) and reduced orgasmic capacity (29–64 %) [56, 57]. In both sexes, bladder and bowel disturbances

Table 2 Summary of fertility, pregnancy and lactation risks of disease-modifying drugs currently approved for treatment of multiple sclerosis

Drug (generic name)	Fertility	Pregnancy	Lactation
Interferon-β	No effects	Exposure was associated with a lower mean birth weight, shorter mean birth length and preterm birth	Excretion in human milk is not well established; the transfer should be limited by the molecular weight; the drug is not orally bioavailable
Glatiramer acetate	No effects	No major concerns after drug exposure during pregnancy	Excretion in human milk is not well established; the transfer should be limited by the molecular weight; the drug is not orally bioavailable
Natalizumab	Reduced fertility in animal studies; no information in humans	Limited information in humans; haematological alterations, lower birth weight, shorter birth length and risks of malformations and miscarriage have been reported	Excretion in human milk has been reported; the drug is not orally bioavailable
Fingolimod	No effects	Limited information in humans; increased risks of miscarriage and malformations have been reported	Excretion in rat milk has been reported; the drug is orally bioavailable
Mitoxantrone	Amenorrhoea and transient azoospermia have been reported	Limited information in humans; increased risk of malformations has been reported	Excretion in human milk has been reported
Cyclophosphamide[a]	Amenorrhoea and azoospermia have been reported	Limited information in humans; increased risk of malformations has been reported	Excretion in human milk has been reported
Teriflunomide	No effects	Embryotoxicity in animal studies in the human therapeutic range	Excretion in rat milk has been reported
Dimethyl fumarate	No effects	Limited information in humans	Excretion in human milk is unknown
Alemtuzumab	No effects	Limited information in humans; thyroid diseases and malformations have been reported	Excretion in mouse milk has been reported

[a] Although cyclophosphamide has not received formal approval, it is widely used in patients with multiple sclerosis

may contribute to affect sexual activity, interfering with social relationships and with intimate behaviour [59].

Endocrinological studies have shown that women with MS have significantly higher follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, and significantly lower oestrogen levels in the early follicular phase of the menstrual cycle [60]. Higher FSH levels in the early follicular phase are strongly related to a lower ovarian reserve. Other studies have reported higher incidence rates of hyperprolactinaemia [60] and hyperandrogenism [60, 61]. More recently, a reduced level of anti-Mullerian hormone (a marker of ovarian reserve and function) has been found in women with MS [62]. These alterations could contribute to the slightly higher incidence of oligo/amenorrhoea observed in women with MS (20 versus 16 % in control subjects) in one of these studies [61]. Moreover, male patients have been reported to have reduced testosteronaemia [59, 63, 64], potentially affecting sperm production, libido and sexual competence. On the other hand, good spermatogenesis may be accomplished even with subnormal testosteronaemia [65].

Despite these alterations in both male and female patients, on the whole, MS does not appear to impair fertility in women with MS [66]. Moreover, infertility is quite frequent in people of child-bearing age, and its association with MS may not be necessarily linked by a cause–effect relationship.

It has to be noted that assisted reproductive techniques using gonadotropin-releasing hormone (GnRH) agonists and gonadotropins are probably related to the occurrence of MRI activity and an increase in the relapse rate following in vitro fertilization [67–69]. Indeed, GnRH affects immune cell proliferation; cytokine, chemokine and endothelial growth factor production; and oestrogen levels.

As for the impact of MS on pregnancy outcomes, there are probably no significant major differences between women with MS and the general population [70–73]. In some studies, a higher frequency of neonates small for gestational age, an increased predisposition to urinary infections and constipation, and a greater intervention to induce labour have been reported, particularly in patients with higher disability levels [70–72, 74–76].

As for the influence of pregnancy on the course of MS, there is consistent evidence that the gestational period is associated with a reduction in the risk of relapses, particularly during the third trimester, whereas the 12-month period after delivery, and especially the first trimester, is characterized by a significant increase in the relapse rate and represents a critical phase for patient counselling and therapeutic decision-making [77, 78]. Indeed, a recent meta-analysis of 13 published studies showed that the risk of relapse during pregnancy decreased on average from a mean value of 0.44 ± 0.02 to 0.18 ± 0.01 ($p < 0.0001$) and increased to 0.70 ± 0.02 in the year after delivery [78]. These patterns could be explained by the immunological effects of changes in circulating pregnancy hormones (oestrogen, progesterone, prolactin and others) [79] and by changes in the expression of inflammation-related genes [80]. The occurrence of postpartum relapses was more frequent in women with a higher EDSS score at conception and a higher relapse rate before and during pregnancy [77, 81, 82]. However, the majority of the studies were conducted before the introduction of DMDs; thus, fewer data on the possible impact of pregnancy on the MS course in the scenario of DMD treatment are available. The MS Study Group of the Italian Neurological Society established a network among the main MS centres, gathering information on pregnancy in MS [83]. In the Italian pregnancy dataset, the occurrence of relapses in the year after delivery was associated with an approximately two-fold increased risk of disability accrual in the year after delivery. On the other hand, the early introduction or resumption of DMDs within the first trimester after delivery marginally reduced the risk of postpartum relapses [82]. More recently, in the large international MSBase registry pregnancy study, exposure to DMDs before conception was independently associated with a lower risk of postpartum relapses [84]. In the absence of a concurrent control group, the information on the overall impact of pregnancy on the MS course and disability remains, however, controversial. In the seminal Pregnancy in Multiple Sclerosis (PRIMS) study, disability progression in the follow-up period was estimated to correspond to what is expected in the general population of MS patients [77, 81]. Recently, a population-based study from the British Columbia MS Clinic found that term pregnancies had no effect on the time to reach an EDSS score of 6.0, which was predicted only by a progressive course and older age at MS onset [85]. A few other studies have even suggested a possibly protective role of pregnancy [86–88]. It is also possible to speculate that, despite the relapse-related disability increase in the year after delivery, the long-term outcome remains largely unaffected by pregnancy. Indeed, over the long-term period, the available evidence does not point to any major deleterious effect of pregnancy on the disease course and, overall, the impact of pregnancy on the MS course does not usually represent a concern when family planning is being considered.

Neither epidural anaesthesia [81, 89] nor caesarean section [89] has been associated with adverse effects on delivery or the postpartum MS course. The role of breast-feeding remains controversial. A protective role of exclusive breast-feeding has been suggested [90, 91], possibly mediated through immunological mechanisms related to lactational amenorrhoea [92]. However, current data obtained in larger samples of patients have indicated a neutral role of breast-feeding. Indeed, when analysed together with other confounders, breast-feeding did not seem to represent a protective factor against the risk of postpartum relapses and may simply reflect a different patient choice depending on disease activity [93, 94]. It is recommended that the use of DMDs be avoided during breast-feeding. Therefore, the decision about whether to introduce a DMD immediately after birth, particularly in women at higher risk of increased disease activity, needs to be weighed against the potential benefits of breast-feeding in the setting of a shared decision-making process.

The remainder of this article provides a review of the available information on the utilization of approved DMDs for the treatment of MS during pregnancy, with a focus on fertility, foetal development, delivery and breast-feeding.

3 Impact of Disease-Modifying Drugs on Fertility, Pregnancy and Childbirth

Since 1979, the FDA has classified drugs under a five-letter system on the basis of their risk during pregnancy in certain categories, or on the basis of such a risk weighed against potential benefit. However, through experience and stakeholder feedback, the FDA learned that the pregnancy categories were confusing and were often misinterpreted and misused. On the other hand, a narrative structure for pregnancy labelling is believed to be better able to capture and convey the potential risks of drug exposure based on animal or human data, or both. Therefore, the FDA determined a final rule that requires the removal of the pregnancy categories from all drug products. This final rule is effective from 30 June 2015 and will be implemented within the next 3–5 years [95]. A similar narrative classification system is required by the EMA [96]. With this background, the present review avoids the use of the FDA letter system and summarizes the available evidence about the impact of DMDs on fertility, pregnancy, foetal development, delivery and breast-feeding.

3.1 Interferon and Glatiramer Acetate

3.1.1 Fertility

On the whole, the information on the impact of DMDs for MS on fertility is scarce. As for IFN, in evaluations of pregnancies occurring during clinical trials of IFN-β1a, the rate of pregnancy was similar in both the treatment and placebo groups [97, 98]. IFN and GA do not seem to alter the sperm count and are usually not withdrawn if a man wants to become a father [99, 100]. However, formal reports on the effects of these drugs on male fertility are lacking.

3.1.2 Pregnancy and Foetal Development

Animal studies on IFN have shown an increased risk of spontaneous abortion, whereas there have been no adequate and well-controlled studies in pregnant women. However, in several post-marketing studies, the spontaneous abortion rate did not seem to be different from that of the general population [101]. In particular, two large registries reported spontaneous abortion frequencies of 11.5 and 8 % of cases, respectively [83, 102]. Moreover, the occurrence of malformations or developmental abnormalities has been described in some studies, but the overall frequency does not seem to be different from that of the normal population [83, 90, 102–104]. Finally, a lower body weight has been observed in some studies [83, 103–105] but not confirmed by others [106, 107]. On the whole, the best evidence (level 3) suggested that IFN exposure was associated with a lower mean birth weight, a shorter mean birth length and preterm birth, but not with spontaneous abortion [101].

As for GA, no major concerns have been reported in relation to drug exposure during pregnancy [90, 101, 103, 104, 108–111]. It has to be noted, however, that the data on GA derive mainly from small-sample studies.

3.1.3 Delivery and Breast-Feeding

With regard to delivery modalities, there are no major concerns related to exposure to immunomodulators. As for breast-feeding, excretion of IFN and GA in human milk is not well established [78, 81, 108, 112]. The transfer of these compounds should be limited by their molecular weight [71]. Moreover, it is likely that they are depolymerized after oral ingestion [106]. In one recent report [113], IFN transfer to human breast milk was assessed in six women receiving intramuscular IFN-β1a. The study found an estimated relative infant dose of 0.006 % of the maternal dose. No side effects were noted in any of the breast-fed infants [113]. Likewise, no adverse events were reported in nine mothers who breast-fed their babies for a mean period of 3.6 months while taking GA [114] and in three mothers taking GA and one mother taking IFN [115]. However, although exposure of the child is not expected, clinical data on the use of GA or IFN formulations during breast-feeding are limited; IFN and GA should be avoided during lactation.

3.2 Natalizumab

3.2.1 Fertility

There are no studies on the effects of natalizumab on human fertility [116, 117]. In preclinical studies, natalizumab was associated with reductions in female guinea pig fertility at dose levels of 30 mg/kg but not at the 10 mg/kg dose level (2.3 times the clinical dose) [118]. Male guinea pig fertility was unaffected at doses up to seven times the recommended human dose [118].

3.2.2 Pregnancy and Foetal Development

Animal studies on natalizumab have shown reduced foetus survival and an increased risk of haematological effects (anaemia, thrombocytopenia), increased spleen weight and reduced liver and thymus weights. Therefore, it should not be used during pregnancy, with the exception of severe active cases. Gathering information on the consequences of natalizumab exposure in pregnancy is of particular relevance, as stopping the therapy prior to pregnancy planning exposes the patients to MS reactivation [119].

A few case reports have shown a normal outcome of pregnancy after natalizumab exposure throughout the whole gestational period [120, 121]. Another study reported mild-to-moderate haematological alterations (mainly thrombocytopenia and anaemia) in 10 of 13 infants whose mothers received natalizumab during the third trimester of pregnancy [122].

A recent paper reported the outcome of 102 pregnancies in women exposed to natalizumab as compared with 95 pregnancies in disease-matched women and 98 pregnancies in healthy control subjects [123]. Exposure was defined as treatment with natalizumab from 8 weeks prior to the start of the last menstrual period and onwards. Natalizumab does not appear to increase the baseline risk of malformations in comparison with disease-matched patients. The mean birth weight and length were significantly lesser in comparison with healthy control subjects (3159 g and 50.3 cm, respectively) but comparable to those observed in disease-matched patients. The rate of spontaneous abortion, however, was significantly higher in exposed pregnancies (17.3 %) and in disease-matched patients (21.1 %) in comparison with healthy control subjects (4.1 %). The risk of miscarriage may still be of concern, and further studies are needed [123].

3.2.3 Delivery and Breast-Feeding

After exposure to natalizumab, a higher rate of caesarean sections have been reported [123]. Excretion of natalizumab into breast milk has been observed in humans [116, 117]. Although natalizumab is not orally bioavailable, the effects of exposure on infants are unknown. Natalizumab should be avoided during lactation.

3.3 Fingolimod

3.3.1 Fertility

The administration of oral fingolimod to male and female rats prior to and during mating had no effect on fertility up to the highest fingolimod dose tested (10 mg/kg, which is approximately 200 times the recommended human dose) [124, 125].

3.3.2 Pregnancy and Foetal Development

Animal studies on fingolimod have shown embryolethality and teratogenic effects [124, 125]. The S1P receptors are involved in vascular formation during embryogenesis, and the most common foetal visceral malformations in rats included ventricular septal defect and persistent truncus arteriosus. A teratogenic effect occurred at doses lower than those recommended in humans.

The EMA product information recommends advising women regarding the potential for serious risk to the foetus and the need for effective contraception during treatment with fingolimod [124, 125]. A wash-out period of at least 2 months is recommended [124, 125]. A recent paper reported the outcomes of 89 pregnancies that occurred during the clinical development programme [126]. The rate of spontaneous abortion (24 %) slightly exceeded that in the general population (15–20 %). Abnormal foetal development was observed in 7.6 % of cases, at the upper limit of that expected in the general population (4–8 %). The reported malformations included one case of acrania, one case of unilateral congenital posteromedial bowing of the tibia and one case of tetralogy of Fallot. The cases of abnormal foetal development, together with preclinical data showing teratogenicity, indicate a potential risk of treatment-related effects [126]. Therefore, it is strongly recommended that pregnancy is avoided during treatment with fingolimod.

3.3.3 Delivery and Breast-Feeding

Studies in rats have provided evidence of excretion of fingolimod into breast milk [124, 125]. Since the drug is orally bioavailable, the use of fingolimod during lactation should be avoided.

3.4 Mitoxantrone and Cyclophosphamide

3.4.1 Fertility

Treatment with mitoxantrone caused long-lasting amenorrhoea linked to a reduction of the ovarian reserve in up to 17.3 % of women under 45 years of age in a large French series [38, 39]. Amenorrhoea was more frequent in women older than 35 years at the commencement of mitoxantrone therapy [38, 39]. In the Italian survey, mitoxantrone-induced amenorrhoea was detected in 26 % of women and increased by 2 %/mg/m^2 of the cumulative dose and by 18 % for each year of age. On the other hand, the administration of oestroprogestinic therapy reduced the risk of amenorrhoea [38]. In men, transient azoospermia was described after NOVP (mitoxantrone, vincristine, vinblastine and prednisone) chemotherapy, with recovery after 3–4 months [127].

Cyclophosphamide exerts a toxic effect on ovarian follicles and finally reduces the ovarian reserve and the availability of female gametes. Cyclophosphamide therapy in MS caused definitive amenorrhoea in up to 33 % of women [42, 44], particularly in women older than 31 years, as well as in long-term therapy. In male patients receiving cyclophosphamide, severe gonadal dysfunction, with transient or permanent azoospermia, is found in 50–90 % [128]. Germinal cells are vulnerable because of their high mitotic activity; the effect appears to be age dependent and dose dependent [129].

3.4.2 Pregnancy and Foetal Development

Studies in animals and humans on mitoxantrone have shown embryotoxicity. The administration of mitoxantrone to rats during the organogenesis period was associated with foetal growth retardation at doses of 0.1 mg/kg/day (0.01 times the recommended human dose) [130]. In rabbits, mitoxantrone treatment increased the rate of premature delivery at doses of 0.1 mg/kg/day (0.01 times the recommended human dose). Moreover, adverse effects on the developing foetus have been observed with structurally related agents [130].

A few case reports have described clinical outcomes of pregnancy exposed to mitoxantrone in patients with MS [131–133]. After exposure until the 29th week of gestation [131], although foetal growth was reduced, the newborn had no evidence of malformations. In another case, exposure to mitoxantrone during conception was associated with Pierre Robin syndrome [131]. In a patient treated with mitoxantrone for acute myeloid leukaemia, there were no

malformations reported. [132]. On the basis of the available information, women of child-bearing potential undergoing mitoxantrone treatment must be counselled to avoid pregnancy and to use effective birth control methods; pregnancy should be excluded before each infusion [130].

As for cyclophosphamide, studies in animals and humans have shown embryotoxicity and foetotoxicity [134]. Animal studies have demonstrated adverse effects on female germ cells, inducing genetic abnormalities. In mice, higher rates of pregnancy failures and malformation have been reported after exposure 1 week before mating [135]. Although, in humans, successful pregnancies after cyclophosphamide treatment for lupus and chronic myeloid leukaemia have been reported [136], other studies have shown a teratogenic effect after exposure during the first trimester. The most common malformations are hydrocephalus, microretrognathia, ectrodactyly, cleft palate and exencephaly [137]. However, a few studies did not show an increased risk of congenital abnormalities among offspring of patients previously treated with cyclophosphamide, suggesting that possibly a long lapse of time between exposure and pregnancy may allow fertility and foetal development to be unaffected [135, 138, 139]. Therefore, use of cyclophosphamide during pregnancy is contraindicated, and it should be withdrawn at least 3 months before the patient tries to conceive [134].

3.4.3 Delivery and Breast-Feeding

There is no information on delivery modalities after exposure of pregnancy to mitoxantrone and cyclophosphamide. Both drugs are excreted into breast milk in humans [130, 134]. Since they can exert significant negative effects on newborns, their use is contraindicated during lactation.

3.5 New Drugs

The information on the influence of new drugs for the treatment of RRMS on pregnancy-related issues is limited to what has been reported in drug monographs [140–145] and in a few conference abstracts [146–149].

3.5.1 Teriflunomide

The results of studies in animals have not shown an effect on fertility. Fertility was unaffected in rats despite adverse effects of teriflunomide on male reproductive organs, including a reduced sperm count [140, 141, 146].

Animal studies have shown embryotoxicity and teratogenicity in rats and rabbits at doses in the human therapeutic range. Adverse effects on the offspring were detected when teriflunomide was administered to pregnant rats during gestation and lactation. However, the risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered to be low [146]. The estimated female plasma exposure via the semen of a treated patient is expected to be 100 times lower than the plasma exposure after 14 mg of oral teriflunomide [140, 141].

Teriflunomide is therefore contraindicated in pregnancy. However, clinical trial experience documented that the outcomes of 83 pregnancies in female MS patients and 22 pregnancies in partners of male patients were consistent with those in the non-MS population [147]. The spontaneous abortion rate was 19 %, and no structural or functional problems were reported [147]. Nevertheless, information in humans is still limited, and women of child-bearing potential have to use effective contraception during and after treatment as long as the teriflunomide plasma concentration is above 0.02 mg/L. In case of pregnancy during treatment, it is possible to rapidly lower the blood level of teriflunomide by means of the accelerated elimination procedure (cholestyramine or activated powdered charcoal). Likewise, for women receiving teriflunomide who wish to become pregnant, the medicine should be stopped and an accelerated elimination procedure should be provided [140, 141].

Animal studies have shown excretion of teriflunomide in breast milk. Therefore, teriflunomide is contraindicated during lactation [140, 141].

3.5.2 Dimethyl Fumarate

Animal studies do not suggest that dimethyl fumarate reduces fertility. Oral administration of dimethyl fumarate to male rats prior to and during mating had no effects on male fertility up to the highest dose tested (375 mg/kg/day, at least two times the recommended dose in humans). Oral administration of dimethyl fumarate to female rats prior to and during mating, and continuing to day 7 of gestation, induced a reduction in the number of oestrous stages per 14 days and increased the number of animals with prolonged dioestrus at the highest dose tested (250 mg/kg/day, 11 times the recommended dose in humans). However, these changes did not affect fertility or the number of viable foetuses produced [142, 143, 148].

Animal studies have shown reproductive toxicity. Dimethyl fumarate has been shown to cross the placental membrane into foetal blood in rats and rabbits, with ratios of foetal to maternal plasma concentrations of 0.48 to 0.64 and 0.1, respectively. No malformations were observed at any dose of dimethyl fumarate in rats or rabbits. Administration of dimethyl fumarate to pregnant rats during the period of organogenesis resulted in maternal adverse effects at four times the recommended dose, and low foetal weight and delayed ossification (metatarsals and hindlimb

phalanges) at 11 times the recommended dose. The lower foetal weight and delayed ossification were considered secondary to maternal toxicity (reduced body weight and food consumption). Oral administration of dimethyl fumarate to pregnant rabbits during organogenesis had no effect on embryo-foetal development and resulted in reduced maternal body weight at seven times the recommended dose and increased abortion at 16 times the recommended dose [142, 143, 148].

To date, the information on pregnancy outcomes after exposure in women with MS is limited. Preliminary information on 45 pregnancies exposed to dimethyl fumarate during clinical trials and 135 pregnancies during the post-marketing phase has been reported [148]. There was no increased risk of foetal abnormalities, and the incidence of spontaneous abortion was consistent with that of the general population [148].

It is unknown whether dimethyl fumarate or its metabolites are excreted in human milk, and a risk to newborns cannot be excluded. Therefore, administration during lactation should be avoided. A decision must be made whether to discontinue breast-feeding or to discontinue dimethyl fumarate, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman [142, 143].

3.5.3 Alemtuzumab

CD52 is known to be present in human and rodent reproductive tissues. In animal studies, treatment with intravenous alemtuzumab at doses up to 10 mg/kg/day, administered for five consecutive days (7.1 times the human exposure at the recommended daily dose) had no effect on fertility and reproductive performance in male mice. The number of normal sperm was significantly reduced (<10 %) relative to that in control subjects, whereas the proportion of abnormal sperm was increased (up to 3 %). However, these changes did not affect fertility and were therefore considered to be non-adverse [144, 145].

There are no adequate clinical safety data on the effect of alemtuzumab on fertility in humans. In 13 male patients receiving alemtuzumab (treated with either 12 or 24 mg), there was no evidence of aspermia, azoospermia, a depressed sperm count, or motility or morphological abnormalities. In female mice dosed with intravenous alemtuzumab up to 10 mg/kg/day (4.7 times the human exposure at the recommended daily dose) for five consecutive days, the average number of corpora lutea and implantation sites per mouse were significantly reduced [144, 145].

Animal studies have shown reproductive toxicity. Placental transfer and potential pharmacological activity of alemtuzumab were observed in mice during gestation and following delivery. In pregnant mice, exposure to intravenous doses of alemtuzumab up to 10 mg/kg/day (2.4 times the human exposure at the recommended dose of 12 mg/day) for five consecutive days increased the risk of foetal death. Alterations in lymphocyte counts were observed in pups exposed to alemtuzumab during gestation at doses of 3 mg/kg/day for five consecutive days (0.6 times the human exposure at the recommended dose of 12 mg/day). Moreover, thyroid diseases, which are frequent side effects of alemtuzumab therapy, pose special risks in women who are pregnant. Hypothyroidism is associated with increased risks of miscarriage and foetal abnormalities. On the other hand, during Graves' disease, maternal thyroid-stimulating hormone receptor antibodies can be transferred to a developing foetus and can cause transient neonatal Graves' disease. Preliminary information on 139 pregnancies in 104 patients has been reported [149]. The rate of spontaneous abortion was 17 %, comparable to rates in the general population. No evidence of teratogenicity emerged. Eleven serious adverse events were reported in foetuses/infants, not suggestive of any emerging pattern. One case (a grade 4 thyrotoxic crisis) was likely related to alemtuzumab exposure [149].

Since serum concentrations were low or undetectable within approximately 30 days following each treatment course, women of child-bearing potential should use effective contraceptive measures during treatment and for 4 months following a course of alemtuzumab [144, 145].

Alemtuzumab has been detected in the milk and offspring of lactating female mice. It is unknown whether alemtuzumab is excreted in human milk, and a risk to the breast-fed child cannot be excluded. Therefore, breast-feeding should be discontinued during each course of treatment with alemtuzumab and for 4 months following the last infusion of each treatment course [144, 145].

4 Conclusions

In recent decades, pregnancy-related issues in MS have received growing interest. On the one hand, MS is more frequent in women than in men, and the female-to-male ratio is increased. On the other hand, the therapeutic options have widened and are being started earlier, since early treatment has been demonstrated to be more effective. Therefore, gathering information on the influences of the available DMDs on fertility, pregnancy and childbirth is of crucial importance for the counselling of MS patients. As for the 'old' immunomodulatory drugs (IFN and GA), there is mounting evidence of the relative safety of pregnancy exposure in terms of maternal and foetal outcomes. In case of higher clinical disease activity before pregnancy, these drugs could be continued until conception. As for natalizumab and fingolimod, the information is more limited.

While fingolimod seems to be associated with an increased risk of foetal malformations, the effects of natalizumab exposure of the pregnancy should be still ascertained. In particular, the risk of miscarriage warrants further assessment. The immunosuppressants mitoxantrone and cyclophosphamide are associated with reduced fertility and reproductive toxicity. Although preliminary evidence in humans seems favourable, the new oral immunosuppressant teriflunomide is contraindicated during pregnancy because of demonstrated foetal toxicity. An accelerated elimination procedure is available in case of unexpected pregnancy or pregnancy planning. As for dimethyl fumarate and alemtuzumab, while animal studies suggest reproductive toxicity, the information on humans is still limited. All of the drugs should be avoided during lactation, since excretion in human milk has been demonstrated or is unknown, and a risk to newborns cannot be excluded. Further effort in the post-marketing phase is required in order to expand our knowledge of treatment-related influences on pregnancy issues and to identify rare adverse events that are undetectable during the clinical development programmes. In this regard, the implementation of multicentre international pregnancy registries is advocated.

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