REVIEW ARTICLE

An overview of pregnancy-related issues in patients with multiple sclerosis

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Keywords:
breastfeeding, multiple sclerosis, pregnancy, relapse

Received 21 November 2014
Accepted 5 June 2015

European Journal of Neurology 2015, **22** (Suppl. 2): 34–39

doi:10.1111/ene.12797

Although pregnancy in women with multiple sclerosis (MS) is not generally considered high risk, there are some associated therapeutic challenges. The pregnancy-associated reduction in the relapse rate, especially in the third trimester, is followed by a sharp increase in the first few months postpartum. Nevertheless, retrospective evidence for pregnant women with and without MS followed for up to 10 years indicates that pregnancy has no perceptible effect on long-term disease course or disability progression. Likewise, MS has no apparent effects on the pregnancy course or fetal outcomes. All disease-modifying therapies (DMTs) have potential adverse effects on fertility and pregnancy outcomes, but the level of risk varies amongst agents. There is some support for continued use of interferon-β and glatiramer acetate throughout pregnancy to reduce the risk of relapse. Use of DMTs during breastfeeding is best avoided if possible. Close evaluation of drug safety information is imperative when managing women with MS who are pregnant or wish to become pregnant. Decision-making should be a shared experience between patient and physician, and the approach must be individualized for each patient.

Introduction

The multiple sclerosis (MS) and pregnancy paradigm has evolved considerably over the past 50 years. In the 1950s and 1960s, women with MS were advised to avoid pregnancy altogether based on limited data from single case reports and small case studies. In the 1970s to early 1990s, women with MS became better informed about the risks of pregnancy through evidence derived from large retrospective studies. The most significant paradigm shift occurred in 1998 when the prospective Pregnancy in Multiple Sclerosis (PRIMS) study reported a reduction in the relapse rate during pregnancy [1]. Beginning in 2000, a new era of early treatment with disease-modifying therapy (DMT) brought about another major change in the approach to pregnancy. At present, discussions with MS patients about pregnancy tend to pivot around the timing of treatment; i.e. can DMTs be used before, at the beginning of, during or after pregnancy?

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Relapse rate and the role of estrogens

The PRIMS study documented a significant reduction in the relapse rate during pregnancy in women with MS, especially in the third trimester, which was followed by a sharp increase in the number of relapses in the immediate postpartum period (Table 1) and a return to the rate recorded in the pre-pregnancy year [1]. Significant predictors of postpartum MS relapse included a higher relapse rate in the pre-pregnancy year, a higher relapse rate during pregnancy and a higher Expanded Disability Status Scale (EDSS) score at pregnancy onset [2]. The PRIMS data were subsequently combined with 12 other studies in a meta-analysis that included 1221 pregnancies in women with MS [3]. The results confirmed a significant

Table 1 Annual relapse rate per woman with multiple sclerosis (MS) before, during and after pregnancy

	Mean (SD) relapse rate	
	[1]	[4]
Pre-conception period	0.7 (0.9)	0.32 (0.02)
First trimester	0.5 (1.3)[a]	0.25 (0.04)
Second trimester	0.6 (1.6)	–
Third trimester	0.2 (1.0)[b]	0.13 (0.03)[c]
First 3 months post-partum	1.2 (2.0)[b]	0.61 (0.06)[c]

[a]$P = 0.03$ vs. year before pregnancy; [b]$P < 0.001$ vs. year before pregnancy; [c]$P < 0.001$ vs. 2 years before pregnancy.

decrease in the relapse rate during pregnancy (0.18 vs. 0.44 before pregnancy; $P < 0.0001$), with an effect size greater than that achieved with currently available therapies, and a significant increase in the relapse rate postpartum (to 0.70; $P < 0.0001$). A more recent study utilizing the international MSBase Registry, in which 893 pregnancies in 674 women with MS were examined, further confirmed the pattern observed in the PRIMS study (Table 1) [4]. The annualized relapse rate in the pre-conception period was found to be the strongest predictor of early postpartum relapse, suggesting that minimizing relapse frequency prior to conception may lead to better early postpartum outcomes.

The most accepted theory to explain the protective effect of pregnancy on the relapse rate and disease activity in women with MS is that, during pregnancy, estrogens and other sex hormones induce immunological changes by changing the T helper (Th) cell profile to predominantly Th2 (anti-inflammatory cytokines) rather than Th1 (pro-inflammatory cytokines); the opposite occurs in the postpartum period. Additional evidence for the protective role of estrogen is provided by an *in vivo* study which demonstrated a reduction in the clinical severity of experimental autoimmune encephalomyelitis following administration of estrogen receptor-alpha ligand in a mouse model of MS [5]. The study also documented reduced inflammatory lesions and demyelination in the white matter of mice treated with estrogen receptor-alpha ligand or estradiol [5]. In a multicenter clinical trial, non-pregnant women with relapsing–remitting MS who had a high-dose estrogen-containing oral contraceptive added to subcutaneous interferon-β1a treatment had a significant ($P < 0.05$) 26.5% reduction in active lesions on brain magnetic resonance imaging (MRI) scan at 96 weeks compared with those who received interferon-β1a alone [6]. Elsewhere it was shown that non-pregnant women with relapsing–remitting MS treated with oral estriol at a pregnancy dose (8 mg/day) had significant decreases from baseline in the number and volume of gadolinium-enhancing lesions on brain MRI [7]. Enhancing lesions returned to pre-treatment levels when estriol was stopped, and decreased significantly again when the hormone was reinstated.

An Australian case–control study has provided interesting data about a cumulative beneficial effect of pregnancy on MS disease onset [8]. Multigravida women were found to be less likely to develop MS, with a 49% reduction in the risk of a first clinical demyelinating event for each child born. The investigators suggested that the current trend towards an older maternal age and fewer children may be contributing to the increasing female excess amongst MS cases over time.

Long-term effects of pregnancy on MS

The impact of pregnancy on the long-term disease course and disability in MS is not yet clearly defined, but appears to be benign. Eight studies have suggested that pregnancy has no effect on long-term outcome in MS [9–16], whereas four other studies indicated that parity was potentially beneficial [17–20]. These studies were limited, however, by methodological weaknesses such as relatively small sample sizes, retrospective data collection, and observational or non-population-based designs. Moreover, since planning and achievement of a pregnancy often depends on the MS course, this could be a confounding factor.

Some support for a protective effect of pregnancy on long-term disability progression in women with MS has come from a recent two-center Italian study [21]. Data for 445 women (261 nulliparous, 184 with pregnancies after MS onset) were analyzed and Cox regression models revealed a lower risk for parous than nulliparous women in reaching disability milestone scores of 4.0 [hazard ratio (HR) 0.552, $P = 0.008$] and 6.0 (HR = 0.422, $P = 0.012$) on the EDSS. Whether this represents a biological/immunological effect or reflects a higher propensity toward childbearing in women with milder disease remains uncertain and is worthy of further investigation.

Elsewhere, a retrospective analysis of pregnant ($n = 254$) and non-pregnant ($n = 423$) cohorts of women with relapsing–remitting MS indicated that, over the long term (up to 10 years), pregnancy had no material impact on rates of relapse and progression to irreversible disability [22].

Effects of MS on pregnancy course and the fetus

Since MS does not markedly increase the risk of pregnancy complications or have negative effects on fetal

outcomes [23,24], in the absence of other relevant issues, pregnancies in the presence of an MS diagnosis are not generally considered high risk. There is evidence from Finland that MS patients have greater need for instrumental delivery than the general population (16.4% vs. 6.5%; $P = 0.0017$) which may need to be taken into account when planning the delivery [23]. Conversely, a retrospective cohort study from Canada found no significant associations between MS and assisted vaginal delivery or Caesarean section, but did note a slightly higher but non-significant risk of adverse delivery outcomes amongst patients with greater levels of disability [24]. Other potential risks identified for pregnant MS patients have been a higher proportion of neonates small for gestational age (not reproduced by the Canadian group) and more frequent induction and operative interventions during delivery [25].

Multiple sclerosis drugs in pregnancy

Despite approval of DMTs for use in MS more than 20 years ago, information about their safety during pregnancy and breastfeeding is limited. Safety information for the current range of approved DMTs relates mainly to the US Food and Drug Administration (FDA) pregnancy and lactation risk categories (Table 2) [26–28]. The FDA announced recently its decision to replace the 'letter system' (A, B, C, D and X) for pregnancy risk categories with a newer system that provides a summary of potential risks, such as structural abnormalities, embryo/fetal/infant mortality, functional impairments or growth problems, associated with use of a drug.

Outside of animal studies, most data regarding the safety of DMTs in pregnancy derives from case series, retrospective or prospective cohort studies, pregnancy registries and safety databases maintained by the manufacturer [27]. A meta-analysis examined 15 studies and 893 pregnancies in MS patients involving *in utero* exposure to interferon-β ($n = 761$), glatiramer acetate ($n = 97$) and natalizumab ($n = 35$) [29]. For interferon-β, fair- to good-quality prospective cohort studies indicated that exposure was associated with lower mean birth weight, shorter mean birth length and preterm birth (<37 weeks), but not with low birth weight (<2500 g), Caesarean delivery, congenital anomaly (including malformation) or spontaneous abortion [29]. Fair-quality studies (mainly small case series) indicated that glatiramer acetate exposure was not associated with lower mean birth weight, congenital anomaly, preterm birth or spontaneous abortion. A single fair-quality prospective cohort study suggested that natalizumab exposure was not associated with shorter mean birth length, lower mean birth weight or lower mean gestational age [29]. Case reports of mitoxantrone have shown evidence of human fetal risk, and animal studies indicate fetal risk with fingolimod and teriflunomide [3].

Based on currently available information, all DMTs have potential adverse effects on fertility and pregnancy outcomes, as well as during breastfeeding [27–30]. In general, patients are advised to discontinue DMTs prior to conception although there are suggestions that interferon-β and especially glatiramer acetate can be continued throughout pregnancy in patients with severe or highly active disease [30]. Interferon-β exposure for up to 4 weeks after conception was not associated with any significant fetal complications, malformations or developmental abnormalities over a median follow-up of 2.1 years [31]; similar results have been reported for glatiramer acetate [32]. Fingolimod should be discontinued 2–3 months prior

Table 2 Pregnancy and lactation categories of disease-modifying therapies approved for multiple sclerosis – the US Food and Drug Administration (FDA) [25–27]

Currently approved agents	FDA pregnancy category[a]	Lactation category[b]
Interferon-β	C	L3
Glatiramer acetate	B	L3
Fingolimod	C	L4
Natalizumab	C	L3
Mitoxantrone	D	L5
Alemtuzumab	C	NA[c]
Anti-CD20 monoclonal antibody	C	NA[c]
Dimethyl fumarate	C	NA[c]
Daclizumab	C	NA[c]
Teriflunomide	X	NA[c]

[a]Category A: Adequate and well controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well controlled studies in pregnant women. Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite the potential risks. Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits may warrant the use of the drug in pregnant women despite the potential risks. Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in the use of the drug in pregnant women clearly outweigh the potential benefits. [b]L1, safest; L2, safer; L3, moderately safe; L4, possibly hazardous; L5, contraindicated. [c]A lactation risk category is not available. Breastfeeding is not recommended during treatment.

to the cessation of contraception [30], whilst data on the discontinuation of natalizumab are still controversial considering the high risk of disease recurrence even during pregnancy [33]. A negative pregnancy test and adequate contraception are required with use of mitoxantrone and teriflunomide in women of childbearing potential [30]. Physicians may also consider use of monthly intravenous high-dose corticosteroid treatment to coincide with the menstrual cycle in women who have discontinued standard DMTs and are attempting to conceive [28]. Likewise, intravenous corticosteroids are a moderately safe treatment approach for patients who experience an acute exacerbation of MS during the second and third trimesters of pregnancy [28].

Postpartum relapse

The increased risk of relapse in the immediate postpartum period suggests that early reinitiation of DMTs may be beneficial, although the optimal time to restart is unclear. In a survey study of neurologists' practice patterns, more than half the respondents reported restarting DMTs immediately after delivery, whilst another 43% reported waiting for one to three menstrual cycles to restart treatment [34]. A small study in women with MS (n = 32) has suggested that exclusive breastfeeding might protect against postpartum relapse [35], but a similar study in a much larger cohort (423 pregnancies in 298 women) failed to reproduce these findings [36]. Any decision regarding the potential benefits of breastfeeding versus reinitiation of DMTs to reduce the risk of postpartum relapse is best taken on a case-by-case basis.

Breastfeeding

Clinical data to inform about the use of DMTs in MS patients during breastfeeding are also limited. Currently available FDA lactation categories are provided in Table 2 [26–29]. Glatiramer acetate has been detected in human milk but, being an amino acid polymer, it is unlikely to be absorbed across the infant's gastrointestinal mucosa [27,30]. Whilst use of glatiramer acetate in breastfeeding is not recommended as such [30], it might be considered in some circumstances; the potential risk–benefit balance would need to be discussed carefully with the patient [27]. Use of interferon-β, natalizumab, mitoxantrone, fingolimod and teriflunomide is not recommended during breastfeeding [27–30]. Intravenous corticosteroids can be used safely to treat postpartum relapse during breastfeeding, but it is suggested that women pump and discard breast milk for 24–48 h after an infusion of high-dose corticosteroids before continuing to nurse their infant [28].

Conclusions

Although pregnancy is associated with an increased risk of relapse immediately postpartum in women with MS, the apparent lack of negative effects on long-term disease course and disability is an important message to impart to patients. Equally important is the lack of effect of MS on pregnancy course and fetal outcomes. With regard to the use of DMTs, data to inform the management of MS patients who are considering pregnancy, or who are pregnant or breastfeeding, are limited, although recent reviews summarizing the current body of evidence [26–29] may provide useful guidance. The increasing complexity of MS treatment highlights the importance of shared decision-making between patient and physician and individualizing the therapeutic options. A new FDA risk classification system for use of drugs during pregnancy and lactation, together with ongoing surveillance programs and drug registry data, are expected to better inform about the relative benefits and risks of treatment options for MS during pregnancy and breastfeeding so as to guide clinical decision-making in the future.

Acknowledgements

The ParadigMS project is sponsored by Genzyme for logistical and organizational purposes. Writing assistance was provided by Kerry Dechant (Content Ed Net, Madrid, Spain), with funding from Genzyme, a Sanofi company, EMEA HQ, Naarden, the Netherlands.

Disclosure of conflicts of interest

Carlo Pozzilli has served on scientific advisory boards for Almirall, Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Teva Neurosciences, has received funding for travel and speaker honoraria from Actelion, Almirall, Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Teva Neurosciences, and has received research support from Bayer Schering, Biogen Idec, Merck Serono, Novartis and Sanofi-Aventis. Maura Pugliatti has served on scientific advisory boards for Bayer Schering and Genzyme, and has received funding for travel or speaker honoraria from Almirall, Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Teva Neurosciences.

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Appendix

The authors write on behalf of the ParadigMS group: a group of European, Asian and Middle East experts in multiple sclerosis comprising Bernd C. Kieseier (Germany), Paolo Gallo (Italy), Nikolaos Grigoriadis (Greece), Eva Havrdova (Czech Republic), Andreas Lysandropoulos (Belgium), Celia Oreja Guevara (Spain), Carlo Pozzilli (Italy), Maura Pugliatti (Italy), Sven Schippling (Switzerland), Vincent van Pesch (Belgium), Bart Van Wijmeersch (Belgium), Mona Akhawajah (Saudi Arabia), Alexey Boyko (Russia), Andrew Chan (Germany), Raymond Hupperts (Netherlands), Ralf Linker (Germany), Maria Pia Sormani (Italy). The content of this publication is based upon an in-depth discussion on this topic by all group members. The views expressed are therefore based on the group members' opinions and do not represent the views of Genzyme, a Sanofi Company, the European Academy of Neurology or the European *Journal of Neurology*.