Disease-modifying drugs for multiple sclerosis in pregnancy

A systematic review

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ABSTRACT

Objective: To systematically review the literature regarding safety of disease-modifying drug (DMD) use during pregnancy on perinatal and developmental outcomes in offspring of patients with multiple sclerosis (MS).

Methods: A PubMed and EMBASE search up to February 2012 was conducted with a manual search of references from relevant articles. Selected studies were evaluated using internationally accepted criteria.

Results: Fifteen studies identified 761 interferon β-, 97 glatiramer acetate-, and 35 natalizumab-exposed pregnancies. Study quality ranged from poor to good; no study was rated excellent. Small sample sizes limited most studies. Compared with data for unexposed pregnancies, fair- to good-quality prospective cohort studies reported that interferon β exposure was associated with lower mean birth weight, shorter mean birth length, and preterm birth (<37 weeks), but not low birth weight (<2,500 g), cesarean delivery, congenital anomaly (including malformation), or spontaneous abortion. Fewer studies of fair quality were available for glatiramer acetate and natalizumab. Glatiramer acetate exposure was not associated with lower mean birth weight, congenital anomaly, preterm birth, or spontaneous abortion. Natalizumab exposure did not appear to be associated with shorter mean birth length, lower mean birth weight, or lower mean gestational age. No studies examined mitoxantrone or fingolimod exposure. One study of paternal DMD use during conception found no effect on gestational age or birth weight. Few studies examined longer-term developmental outcomes.

Conclusion: Further studies are needed to determine the potential risks associated with preconceptional and in utero DMD exposure in patients with MS. Discontinuation of DMDs before conception is still recommended. *Neurology*® 2012;79:1130–1135

GLOSSARY

DMD = disease-modifying drug; **GA** = glatiramer acetate; **IFN-β** = interferon β; **ILCOR** = International Liaison Committee on Resuscitation; **MS** = multiple sclerosis.

Multiple sclerosis (MS) is a chronic degenerative disease of the brain and spinal cord, typically affecting young adults.[1] Several disease-modifying drugs (DMD) including interferon β (IFN-β) 1a and 1b, glatiramer acetate (GA), natalizumab, mitoxantrone, and fingolimod are licensed worldwide to reduce the frequency of clinical attacks with the hope of slowing disability progression.[2,3] Women with MS are typically advised to discontinue DMD treatment before conceiving to minimize the risk of fetal harm[4]; nonetheless, prenatal DMD exposure still occurs, in part because approximately 50% of pregnancies are unplanned.[5] To our knowledge, no equivalent guidelines exist for men. Based on animal studies and limited human data (mostly observational postmarketing surveillance studies),[6] the US Food and Drug Administration has classified GA[7] as pregnancy risk category B (no risk shown in animal studies; no adequate human studies).[8] IFN-β,[9,10] natalizumab,[11] and fingolimod[12] as category C (risk shown in animal studies; no adequate human studies),[8] and mitoxantrone[13] as category D (positive evidence of human fetal risk).[8] We systematically reviewed studies investigating the

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safety of DMD exposure on the immediate perinatal and longer-term developmental outcomes in children of patients with MS.

METHODS Evidence evaluation template. The International Liaison Committee on Resuscitation (ILCOR) 2010 Evidence Evaluation Template[14] was used. This is a validated tool for assessing systematic reviews endorsed by 11 international bodies on cardiovascular health and meets all criteria from "a measurement tool for the 'assessment of multiple systematic reviews' (AMSTAR)."[15]

Research question. In men or women with MS, does periconceptional or in utero exposure to IFN-β, GA, natalizumab, mitoxantrone, or fingolimod have an effect on perinatal and developmental outcomes in offspring compared with no periconceptional or in utero exposure?

Search strategy. PubMed (1947–February 2012) and EMBASE (1980–February 2012) were searched using the keywords: MS AND [interferon beta; glatiramer acetate; natalizumab; mitoxantrone; fingolimod] AND [pregnancy; conception; child development; spermatozoa; ovum; reproduction; birth; delivery; fetal; neonatal; obstetric]. Alternative terms identified via either database were also included. Keywords were exploded and selected from MeSH terms for PubMed or advanced keyword searches for EMBASE. References from relevant articles were also searched manually. To avoid overlooking important emerging research, we also searched 2010 and 2011 proceedings from the largest conferences covering MS research (the annual meetings of the American Academy of Neurology and the European and Americas Committees of Treatment and Research in Multiple Sclerosis) as a discussion point only, not in the data analysis.

Inclusion and exclusion criteria. We included studies with the a priori aim of assessing perinatal or developmental outcomes in offspring of men or women with MS exposed to one of the following DMDs during pregnancy of conception: IFN-β (1a and 1b), GA, natalizumab, mitoxantrone or fingolimod. Congenital anomalies included any structural or functional abnormalities present at birth, resulting from malformation, deformation, disruption, or dysplasia. Only English language, peer-reviewed original manuscripts with human subjects were

Table 1 Summary of studies examining DMD exposure during pregnancy and conception in MS

Country (publication year)	Study design; target MS patients	DMD type and no. of exposed pregnancies	Definition of DMD exposure	Average duration of DMD exposure
Argentina (2009)[19]	Retrospective cohort; women	23 DMD (IFN-β, GA)	Within 15 days before conception or during pregnancy	4 wk (mean)
Brazil (2009)[24]	Case series[a]; women	17 IFN-β, 15 GA	During pregnancy	12 patients exposed to GA throughout pregnancy; no information on IFN-β exposure
Brazil (2010)[25]	Case series; women	11 GA	During pregnancy	8.4 mo (mean)
Brazil (2011)[26]	Case series; women	99 DMD (69 IFN-β, 20 GA, 10 other)	During pregnancy	8 wk (mean)
Canada (2005)[16]	Prospective cohort; women	23 IFN-β	During pregnancy	9 wk (mean)
Canada (2011)[20]	Retrospective cohort; women	21 DMD (15 IFN-β, 6 GA)	Within 1 month before conception or during pregnancy	7.2 wk (mean)
Germany (2009)[6]	Prospective cohort; women	69 IFN-β, 31 GA	During pregnancy	IFN-β: 8.8 wk (median) GA: 6.9 wk (median)
Germany (2010)[21b]	Retrospective cohort; men	46 DMD (IFN-β, GA, natalizumab, methotrexate, azathioprine) to fathers only	Conception	Not applicable
Germany (2011)[17b]	Prospective cohort; women	35 natalizumab	Within 8 wk before last menses (ie. ~10 wk before conception) or during pregnancy	6 patients had last infusion 21.3 d (mean) before the LMP; 29 patients had last infusion 22.6 days (mean) after LMP
Italy (2008)[22c]	Retrospective cohort; women	14 IFN-β	During pregnancy	9.1 wk (mean)
Italy (2010)[18b,d]	Prospective cohort; women	88 IFN-β	Within 4 wk before conception or during pregnancy	4.6 wk (mean)
Spain (2007)[23b]	Retrospective cohort; women	34 DMD (unspecified)	During pregnancy	5.4 wk (mean)
United Kingdom (2010)[27c]	Case series; women	14 GA	During pregnancy	31.9 wk (mean)
Europe and North America (2005)[28d]	Case series[a]; women	41 IFN-β-1a	Within 2 wk before conception or during pregnancy	16 patients within 1–4 wk; 3 within 5–8 wk; 1 within 16 wk
Worldwide (mainly Europe and North America) (2011)[29b,d]	Case series[a]; women	425 IFN-β-1a	During pregnancy	4 wk (mean)

Abbreviations: DMD = disease-modifying drug; GA = glatiramer acetate; IFN-β = interferon β; LMP = last menstrual period; MS = multiple sclerosis.
[a] Patients were compared with population estimates instead of individual subjects recruited as controls.
[b] Studies with potential conflicts of interest due to direct funding support from the pharmaceutical manufacturer.
[c] Studies with unknown/unclear conflicts of interest.
[d] Studies with potential conflicts of interest due to employment of author by the pharmaceutical manufacturer.

considered for data analysis. No relevant systematic reviews or meta-analyses were identified.

Data analysis. The level and quality of evidence were determined by the study design, sample size, potential bias, statistical analysis, use of controls, and data collection strategy[14] (tables e-1 and e-2 on the *Neurology*® Web site at www.neurology.org). Potential conflicts of interest were noted but were not included in the quality assessment. Each DMD was assigned an ILCOR Class of Recommendation regarding its use during pregnancy (table e-3). Articles were independently selected and reviewed by E.L. and B.W.W., and consensus on disagreements was reached between H.T., E.L. and B.W.W.

Standard protocol approvals, registrations, and patient consents. Published data were used for this systematic review; hence, no ethical approval was sought.

RESULTS

Search results. PubMed yielded 237 hits and EMBASE 278, with 461 unique citations identified. A total of 15 studies were selected (4 prospective cohort,[6,16-18] 5 retrospective cohort,[19-23] and 6 case series[24-29] studies) for a total of 761 IFN-β-, 97 GA-, and 35 natalizumab-exposed pregnancies. Study characteristics are summarized in tables 1 and e-4. From the 15 studies analyzed, there were more negative than positive findings reported, and most studies did not appear to have potential conflicts of interest. However, studies with negative findings appeared more likely to have had industry funding support. Overall, the level of evidence ranged from Level 3 to 5 (prospective cohort to case series), and the quality ranged from poor to good (table 2).

Perinatal outcomes based on best evidence. ***IFN-β.*** Maternal exposure studies reported mixed findings regarding the risk of lower mean birth weight,[6,16,18,22] lower mean gestational age,[16,22] preterm birth,[6,18] and spontaneous abortion.[6,18] However, the best evidence (good-quality, Level 3) suggested that IFN-β exposure was associated with lower mean birth weight, shorter mean birth length, and preterm birth (<37 weeks) but not with spontaneous abortion, cesarean delivery, or low birth weight (defined as <2,500 g) (table 3).[18] Fair-quality level 3 evidence studies showed no increased risk of lower mean gestational age[16] or congenital anomalies[6] in IFN-β-exposed births (table 3). Descriptively, the incidence of therapeutic abortion was higher in IFN-β-exposed vs IFN-β-unexposed pregnancies but lower than that for the general population.[18,22,28]

GA. Based on fair-quality Level 3 evidence, GA exposure was not associated with lower mean birth weight, lower mean gestational age, preterm birth (<37 weeks), congenital anomaly, or spontaneous abortion (table 3).[6]

Natalizumab. From only one fair-quality Level 3 evidence study of natalizumab, exposure was not associated with shorter mean birth length, lower mean birth weight, or lower mean gestational age (table 3).[17]

Mitoxantrone and fingolimod. No identified studies assessed the safety of mitoxantrone or fingolimod exposure.

Paternal DMD use. Forty-six pregnancies were fathered by 32 men with MS who conceived offspring while being treated with a DMD, resulting in birth weights and lengths comparable to those of the general population (table 1).[21] Descriptively, the risk of congenital anomaly and spontaneous abortion was similar to those for pregnancies of mothers from the general population.[21]

Developmental outcomes. Two studies reported no increased risk of developmental abnormalities associated with IFN-β exposure,[18,22] although follow-up was limited to 1 year in one study[22] and a median follow-up of 2.1 years in the other.[18] One developmental abnormality (inadequate language performance) was described in a case series (Level 5 evidence) of 11 newborns exposed to GA for at least 7 months of gestation.[25] No other studies examining longer-term developmental outcomes were found.

Table 2 Classification of studies based on level and quality of evidence[a]

	Level of evidence		
Quality of evidence	**3: Prospective cohort**	**4: Retrospective cohort**	**5: Case series**
Good	Italy (2010)[18]		
Fair	Canada (2005)[16]	Canada (2011)[20]	Brazil (2009)[24]
	Germany (2009)[6]	Italy (2008)[22]	Brazil (2010)[25]
	Germany (2011)[17]	Spain (2007)[23]	Brazil (2011)[26]
			Europe and North America (2005)[28]
			Worldwide (mainly Europe and North America, 2011)[29]
Poor		Argentina (2009)[19]	United Kingdom (2010)[27]
		Germany (2010)[21]	

[a] See Tables e-1 and e-2 for detailed level and quality of evidence criteria adapted from the International Liaison Committee on Resuscitation evidence evaluation template.

DISCUSSION

Based on an overall assessment of the literature, the following class of recommendation[14] was assigned to each DMD for the following reasons:

- IFN-β: Class III. Evidence from some studies suggests potential harm, specifically lower mean birth weight, shorter mean birth length and preterm birth.
- GA: Indeterminate. Further research is needed because results are not compelling; 3 of the 4 existing human studies of GA were small case series.
- Natalizumab: Indeterminate. Further research is needed because results are not compelling.

Table 3 Perinatal outcomes from the better quality studies (fair and good) comparing DMD-exposed and DMD-unexposed mothers with MS and the level of evidence[a]

	Interferon β			Glatiramer acetate			Natalizumab		
Outcome	Increased risk	Evidence level and quality[b]	OR (95% CI) or *p* value	Increased risk	Evidence level and quality[b]	OR (95% CI) or *p* value	Increased risk	Evidence level and quality[b]	OR (95% CI) or *p* value
Shorter birth length, mean	Yes	3, good	$p < 0.0001$, propensity-score adjusted[18]	Unknown			No	3, fair	$p > 0.05$, unadjusted[17]
Lower birth weight, mean	Yes	3, good	$p < 0.0001$, propensity-score adjusted[18]	No	3, fair	$p > 0.05$, adjusted[6]	No	3, fair	$p = 0.07$, unadjusted[17]
Low birth weight (<2,500 g)	No	3, good	1.14 (0.41–3.15), propensity-score adjusted[18]	Unknown			Unknown		
Cesarean delivery	No	3, good	0.84 (0.49–1.44), propensity-score adjusted[18]	Unknown			Unknown		
Congenital anomaly	No[c]	3, fair	0.9 (0.17–2.88), unadjusted[6]	No[c]	3, fair	$p > 0.05$, unadjusted[6]	Unknown		
Lower gestational age, mean	No	3, fair	$p > 0.05$, unadjusted[16]	Unknown			No	3, fair	$p > 0.05$, unadjusted[17]
Preterm birth (<37 wk)	Yes	3, good	2.11 (1.18–3.78), propensity-score adjusted[18]	No	3, fair	$p > 0.05$, unadjusted[6]	Unknown		
Spontaneous abortion	No	3, good	1.08 (0.40–2.89), propensity-score adjusted[18]	No	3, fair	$p > 0.05$, unadjusted[6]	Unknown		

Abbreviations: CI = confidence interval; DMD = disease-modifying drug; MS = multiple sclerosis; OR = odds ratio.
[a] No study was rated as excellent. See Tables e-1 and e-2 for detailed level and quality of evidence criteria adapted from the International Liaison Committee on Resuscitation Evidence Evaluation Template. Case series studies were not used to complete this table because of the absence of a suitable control group for comparison. We assumed that $p > 0.05$ when studies commented in their Results or Discussion sections that there was no difference between the groups but did not specifically provide an OR or *p* value.
[b] Level of evidence: 3 = prospective cohort study.
[c] This study was probably underpowered (IFN-β n = 69 and GA n = 31)[6] to adequately assess the risk of congenital anomaly because the incidence is approximately 3% in newborns from the general population.[30]

- Mitoxantrone: Class III. Animal studies and human case reports suggest potential harm with no controlled human studies to date.
- Fingolimod: Indeterminate. Further research is needed because the drug only recently entered the market.

Evidence on other DMDs, paternal exposure to DMDs around the time of conception (poor-quality, Level 4 evidence),[21] or longer-term developmental outcomes[18,20,24] remains extremely limited.

Of interest, although most pregnant women with MS exposed to IFN-β discontinued therapy early in pregnancy, IFN-β was associated with prematurity and decreased fetal growth, outcomes often associated with adverse events occurring later in pregnancy. Because the first trimester of pregnancy is characterized by rapid cell division and precisely choreographed gene expression that lays the foundation for later fetal growth and development,[31] it is entirely possible that early IFN-β exposure may have affected these early processes to cause later prematurity and decreased growth.

Emerging research (published in abstract form only) from 2010 and 2011 conference proceedings regarding IFN-β and GA exposure during pregnancy,[32-35] has been largely consistent with the analyzed results of this systematic review. For natalizumab, a case series of 277 exposed pregnancies to mothers with MS found 31 spontaneous abortions and 23 congenital anomalies.[36] For fingolimod, 34 exposed pregnancies resulted in 1 case of tibial malformation, 1 case of tetralogy of Fallot (a congenital heart defect), and 5 spontaneous abortions[37]; authors from both studies concluded that small numbers limited conclusions at present.[36,37]

Women with MS should still be advised to discontinue DMDs if they are planning to conceive. After unintentional DMD exposure during pregnancy, women should consider discontinuation of their MS drugs. However, mitoxantrone aside, there is currently a lack of evidence to strongly support consideration of pregnancy termination after paternal or maternal exposure to the MS DMDs. Future research should further explore long-term development in offspring exposed to DMDs.

AUTHOR CONTRIBUTIONS

E. Lu: design and conceptualization of the study, analysis and interpretation of the data, drafting and revising the manuscript. B.W. Wang: analysis and interpretation of the data, revising the manuscript. C. Guimond: interpretation of the data, revising the manuscript. Dr. Synnes: design of the study, interpretation of the data, revising the manuscript. Dr. Sadovnick: conceptualization of the study, interpretation of the data, revising the manuscript. Dr. Tremlett: design and conceptualization of the

study, analysis and interpretation of the data, drafting and revising the manuscript.

DISCLOSURE

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Thank you, Dr. John F. Kurtzke!

The Neurology online archive has recently been updated to include the following seminal articles related to early research in MS:

Rose AS, Kuzma JW, Kurtzke, JF, et al. Cooperative study in the evaluation of therapy in multiple sclerosis; ACTH vs placebo in acute exacerbations. Neurology 1968 (June); 18 (6 Part 2): 1–10.

Rose AS, Kuzma JW. A protocol for a cooperative study to evaluate the therapeutic effectiveness of ACTH on multiple sclerosis in acute exacerbations. Neurology 1968 (June); 18 (6 Part 2): 1–20 + study forms.

Rose AS, Kuzma JW, Kurtzke, JF, et al. Cooperative study in the evaluation of therapy in multiple sclerosis: ACTH vs. placebo – final report. Neurology 1970 (May); 20 (5 Part 2) 1–59.

Kurtzke, JF. Multiple Sclerosis: What's in a name? Neurology 1988;38:309–316.

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