Pregnancy Studies Assessing Drug Exposure in Populations With Multiple Sclerosis

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CONFLICT OF INTEREST

W. Krueger, M. Anthony, C. Saltus, A. Margulis, and E. Andrews are full-time employees of RTI Health Solutions, which received funding from F. Hoffmann-La Roche Ltd. Real World Data Science to conduct this study. The contract between RTI Health Solutions and the sponsor includes independent publication rights. RTI conducts work for government, public, and private organizations, including pharmaceutical companies. B. Monz and C. Hirst are employees of F. Hoffmann-La Roche Ltd. Real World Data Science.

BACKGROUND

- Because multiple sclerosis (MS) often affects younger women of childbearing potential, women with MS who choose to become pregnant or who experience an unplanned pregnancy must consider the relative benefits and risks of MS disease-modifying therapy.
- Upon making a new treatment available to women of childbearing potential, its safety to mother, fetus, and infant is of key interest. Different study approaches are available (e.g., prospective pregnancy registries, studies using existing health records), each with strengths and limitations.

OBJECTIVE

- To identify the approaches used for pregnancy safety studies among women with MS using disease-modifying therapies and to outline their strengths and weaknesses, in terms of the ability to adequately quantify risks to mother, fetus, and infant.

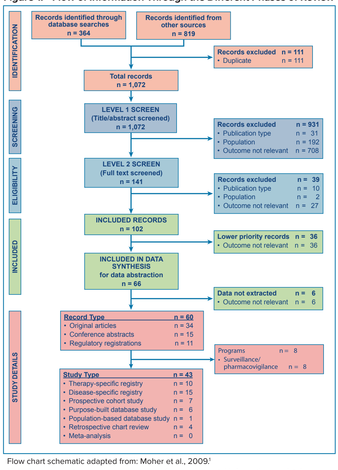
METHODS

- A systematic search was conducted of peer-reviewed published literature (January 1993-October 2015); conference abstracts (two most recent proceedings) from Americas Committee for Treatment and Research in Multiple Scleroses, European Committee for Treatment and Research in Multiple Sclerosis, the Consortium of Multiple Sclerosis Centers, and the American Academy of Neurology; and the following websites: Food and Drug Administration, European Medicines Agency, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, ClinicalTrials.gov, National Multiple Sclerosis Society, and Multiple Sclerosis International Federation.
- Abstracts were independently reviewed by two researchers, and the full-text of selected articles and information was screened by one researcher to determine eligibility for inclusion.
- For inclusion, studies had to be noninterventional, investigate pregnant women diagnosed with MS and treated with a medication used to treat MS, and evaluate at least one of the following outcomes: pregnancy outcomes (e.g., live births, spontaneous abortions, terminations), fetal outcomes (e.g., malformations), offspring outcomes (development abnormalities), obstetric complications, or birth complications.

RESULTS

- A total of 43 studies were identified. Figure 1 details the study types.

Figure 1. Flow of Information Through the Different Phases of Review



Flow chart schematic adapted from: Moher et al., 2009.[1]

Note: Lower priority records were retained for supplemental information on database methods or study design.

DISCUSSION

- Many different approaches have been used to study the impact of medication exposure on pregnancy and infant outcomes among women with MS.
  - Most medications have been investigated using multiple study approaches (Table 1).
  - Most sponsors have conducted (or are conducting) therapy-specific registries (Table 2).
  - Most studies had a limited number of drug-exposed pregnancies and were therefore not informative about drug safety during pregnancy (Table 3).
  - Several registries were unable to reach planned recruitment targets (Table 1).
  - Details of study design were often not reported fully, particularly planned study size and justification.
  - Very few studies have used retrospective analysis of existing population-based medical or health care databases (Table 1).
  - Investigated outcomes and their definitions varied across studies.
  - Data on infant health were very scarce.
  - Fewer than half of studies had internal comparator groups (Table 3).

CONCLUSIONS

- Prospective observational pregnancy exposure studies among women with MS are limited by small study populations; lack of internally sourced unexposed populations for comparison (disease matched and/or healthy populations); long study durations due to slow enrollment, no long-term follow-up data to assess effects of maternal exposure on offspring, including developmental progress.
- Few studies provided robust risk estimates, even many years after initial marketing authorization.
- Drug exposure is expected to be rather short term due to stopping prior to or early in pregnancy, which may hamper enrollment in prospective studies.
- Alternative study designs for future exploration include the following:
  - Disease-specific prospective registries that include data for a large MS population and can study pregnancy and infant outcomes for all MS therapies, including the impact of treatment transitions
  - Retrospective database studies using large population-based health care data that include linkage between mother and offspring, such as multidatabase or multinational studies in which database-derived results are combined for increased study size and precision of estimates

REFERENCES

Please see handout for complete reference list.

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RESULTS

Table 1. Study Types by Multiple Sclerosis Treatment

MS Treatment	Prospective Therapy-Specific Registry	Prospective Disease-Specific Registry	Other Prospective Study	Retrospective Chart Review	Retrospective Database Study
Alemtuzumab	✓		✓		
Dimethyl fumarate	✓				
Fampridine, dalfampridine	✓				
Fingolimod	✓				
Glatiramer acetate		✓	✓	✓	
Interferon β-1a (Biogen)	✓				
Interferon β-1a (EMD Serono)	✓				
Interferon β-1b	✓				
Interferon β (all)		✓	✓		
Intravenous immunoglobulin		✓			✓
Natalizumab	✓	✓			
Peginterferon β-1a	✓				
Teriflunomide	✓	✓			
All disease-modifying therapies		✓	✓	✓	✓

Table 2. Results for Prospective Industry-Sponsored Therapy-Specific Registries

MS Treatment	Marketing Authorization		Study Period		Earliest Publication or Abstract	Study Size		Internal Comparator	Spontaneous Abortion	Congenital Malformation
	US	EU	Planned	Actual		Planned	Actual			
Alemtuzumab[2]	2001	2013	2014-21	Planned	None	185	Planned	NR	N/A	N/A
Dimethyl fumarate[3,4]	2013	2014	2013-21	2013-	2015 (Abstract)	310-375	Ongoing	No	1/4 (25%)	0/3 (0%)
Dimethyl fumarate and peginterferon β-1a[3,4]	2013 2014	2014	2013-23	2013-	None	310-375 (each drug)	Ongoing	No	NR	NR
Fampridine, dalfampridine[6]	2010	2011	2012-16	2012-15	None	375	NR	No	NR	NR
Fingolimod[7-9]	2010	2011	2012-18	2012-	2012 (Abstract)	500	Ongoing	No	3/33 (9%)	1/26 (4%)
Interferon β-1a (Biogen)[10-13]	1996	1997	2004-10	2004-11	2010 (Abstract)	300	329	No	28/306 (9%)	17/272 (6%)
Interferon β-1a (EMD Serono)[14]	2002	1998	2002-08	2002-08	None	300	34	Yes	Exposed: 2/32 (6%) Unexposed: 0/2 (0%)	Exposed: 0 Unexposed: 0
Interferon β-1b[15,16]	1993	1995	2006-10	2006-12	2014 (Article)	420	113	No	11/96 (11%)	5/86 (6%)
Natalizumab[17,18]	2004	2006	2007-15	2007-12	2009 (Abstract)	300	376	No	34/362 (9%)	28/314 (9%)
Teriflunomide[19]	2012	2013	2015-22	2015-	None	196	Ongoing	No	NR	NR

EU = European Union; N/A = not available; NR = not reported; US = United States.

[a] This multiple-drug registry was established to follow pregnant women with exposure to dimethyl fumarate or peginterferon β-1a.

Table 3. Summary of Other Registries and Studies

Registry/Institution	MS Treatment	No. Exposed	No. Comparators	Pregnancy Outcome	Congenital Malformation	Publication Year
Prospective disease-specific registries						
German MS Pregnancy Database	Glatiramer acetate[20]	110 pregnancies	95 DM unexposed pregnancies	✓	✓	2014
	Interferon-β[21]	17 pregnancies	Uncontrolled study	✓		2009
	Intravenous immunoglobulin[22]	51 women	22 DMT exposed women 51 DM unexposed women		✓	2009
	Natalizumab[23]	35 women	23 DM unexposed women	✓	✓	2011
	Natalizumab[24]	74 pregnancies	Uncontrolled study	✓	✓	2012
	Natalizumab[25]	12 women	Uncontrolled study	✓	✓	2014
	Natalizumab[26]	101 women	78 DM unexposed women 98 healthy women	✓	✓	2015
	DMTs[27]	32 men	41 DM interferon-β exposed women 75 DM unexposed women 75 healthy women	✓	✓	2010
	DMTs[28]	119 women	216 DM unexposed women		✓	2012
The Italian Pregnancy Dataset	Glatiramer acetate[29]	17 women	87 DM interferon-β exposed women 311 DM unexposed women	✓		2012
	Interferon-β[30]	87 women	124 DM previously treated women 194 DM unexposed women	✓		2010
	Natalizumab[31]	32 women	88 DM interferon-β exposed women	✓		2014
	DMTs[32,33]	45 men	33 DM unexposed men	✓	✓	2014
	DMTs[34]	415 women	Uncontrolled study	✓		2014
Mother To Baby (US)	Teriflunomide[35,36]	NR	NR	NR	NR	None
Prospective cohort studies						
University of Cambridge, UK	Alemtuzumab[37]	12 women, 6 men	Uncontrolled study	✓	✓	2015
Wirral University Teaching Hospital, UK	Glatiramer acetate[38]	13 women	Uncontrolled study	✓	✓	2010
University of Catania, Italy	Interferon-β[39]	14 women	7 DM previously exposed women 17 DM unexposed women	✓		2008
Hospital for Sick Children, Canada	Interferon-β[40]	16 women (14 with MS)	12 DM unexposed women 18 healthy women	✓	✓	2005
St. Vincent's Hospital, 12 EU countries	None (effect of MS on pregnancy)[41]	241 women	Uncontrolled study	✓	✓	1998
University of Turku, Finland	None (effect of MS on pregnancy)[42]	61 pregnancies	55,547 unexposed pregnancies (Finnish Birth Register)	✓	✓	2010
Berlin Institute for Clinical Teratology and Drug Risk, Germany	DMTs[43]	100 pregnancies	64 DM unexposed pregnancies 1,556 healthy pregnancies	✓	✓	2009
Retrospective chart reviews						
University of Catania, Italy	Cyclophosphamide[44]	11 pregnancies	Uncontrolled study	✓	✓	2014
Academic and private institutions in Brazil	Glatiramer acetate[45]	11 women	Uncontrolled study	✓	✓	2010
Multiple institutions in Argentina, Brazil, Mexico, UK	DMTs[46]	61 pregnancies	89 DM unexposed pregnancies	✓		2013
8 MS referral centers in Buenos Aires, Argentina	DMTs[47]	35 women	46 DM unexposed women	✓	✓	2009
Population-based retrospective database study						
British Columbia MS database and British Columbia Perinatal Database Registry, Canada	DMTs[48]	21 births	80 DM previously exposed births 317 DM unexposed births	✓	✓	2012
Purpose-built retrospective database studies						
Database of Pregnancy and MS, Brazil	All MS drugs[49]	34 pregnancies	15 DM unexposed pregnancies	✓	✓	2009
	DMTs[50]	99 pregnancies	43 DM unexposed pregnancies	✓	✓	2011
	DMTs[51]	85 women	95 DM unexposed women	✓		2013
European Blood and Marrow Transplantation's ProMISE	Autologous hematopoietic stem-cell transplantation[52]	15 women (7 with MS)	Uncontrolled study	✓	✓	2015
MS Center Database, Israel	Intravenous immunoglobulin[53]	28 women	41 DM women treated postpartum 39 DM unexposed women	✓	✓	2004
Database from 16 hospitals, Spain	DMTs[54]	34 pregnancies	54 DM unexposed pregnancies	✓	✓	2007

DM = disease matched; DMT = disease-modifying therapies; UK = United Kingdom.

Table 4. Strengths and Limitations of Various Study Designs Noted From the Reviewed Articles

Study Type	Prospective Therapy-Specific Registries (N = 10)	Prospective Disease-Specific Registries (N = 15)	Prospective Cohort Studies (N = 7)	Retrospective Database Studies (N = 7)	Retrospective Chart Reviews (N = 4)
Strengths					
Follow-up via standardized interviews	✓	✓	✓		
Perceived to be independent of sponsor		✓	✓	✓	✓
Data tailored to sponsor/regulatory concerns/needs	✓				✓
Comparators available		✓	✓	✓	✓
Pregnancy results likely available early				✓	✓
Adjudication of outcomes may be possible	✓	✓	✓		
Systematic data collection	✓	✓	✓		
Limitations					
Small study size	✓	✓	✓		✓
Long study period	✓	✓	✓		
Early outcomes likely underreported	✓	✓	✓		
Volunteer bias	✓	✓	✓		
Loss to follow-up	✓	✓	✓		
Reliance on patient-reported data	✓	✓	✓		
Can be resource intensive	✓	✓	✓		✓
Other limitations	• Lack of a comparator group			• Demographic and covariate data often limited • Timing of medication exposure and postnatal evaluations generally not available • Specific congenital malformations can be difficult to determine without validation	• Mother-infant linkage may be problematic • Clinical site for pregnancy and MS care may be different, resulting in limited data

Presented at: 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 25-28, 2016, Dublin, Ireland