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CONFLICT OF INTEREST

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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

METHODS

• 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.

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	✓		\checkmark		
Dimethyl fumarate	✓				
Fampridine, dalfampridine	✓				
Fingolimod	✓				
Glatiramer acetate		✓	\checkmark	\checkmark	
Interferon β-1a (Biogen)	✓				
Interferon β-1a (EMD Serono)	✓				
Interferon β-1b	✓				
Interferon β (all)		✓	\checkmark		
Intravenous immunoglobulin		✓			✓
Natalizumab	✓	✓			
Peginterferon β-1a	✓				
Teriflunomide	\checkmark	\checkmark			
All disease-modifying therapies		✓	\checkmark	\checkmark	\checkmark

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

	Mark Author	eting ization	Study I	Period	Earliest Publication St		/ Size	Internal	Spontaneous	Congenital
MS Treatment	US	EU	Planned	Actual	or Abstract	Planned	Actual	Comparator	Abortion	Malformation
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 ^{5,a}	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

- 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



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

Projective disease-spectra registricGalarian registricCala (Diregrandia)SD Unregrandia (Lingerandia)SD Unregrandia (Linger	Registry/Institution	MS Treatment	No. Exposed	No. Comparators	Pregnancy Outcome	Congenital Malformation	Publication Year
Interface Interface Interface Interface Interface Interface Interface Interface Interface Interface 	Prospective disease-specif	ic registries					
Interferon P IP programes Uncontrolect study IP		Glatiramer acetate ²⁰	110 pregnancies	95 DM unexposed pregnancies	\checkmark	\checkmark	2014
Introcessing Bandware Function Structure Structure Structure Structure Structure Matalaxamb ²⁰ Structure Structure Structure Matalaxamb ²⁰ Structure Str		Interferon-β ²¹	17 pregnancies	Uncontrolled study	✓		2009
German MS Programmy Database Findman applicability 9 women 2 10 unergoord women - - 2019 Natalizumabil 13 women 2 10 unergoord women - - 2011 Natalizumabil 12 women 2 10 unergoord women - - 2011 Natalizumabil 10 women 2 10 unergoord women - - 2011 Natalizumabil 10 women 2 10 unergoord women - - 2010 Mathile mathing of the state of the proposed women - - 2010 - 2010 Mathile mathing of the state of the proposed women - - 2010 - 2012 Mathile mathing of the state of the		Intravenous		22 DMT exposed women			
Autolizionabi?35 women23 DM unegoode women		immunoglobulin ²²	51 women	51 DM unexposed women		\checkmark	2009
Attalizement MS Program of Database Natalizemable 24 program of Management Part of Manage		Natalizumah ²³	35 women	23 DM unexposed women	✓	✓	2011
Genum No. Programmy Database Machine Server (Maintermote) 1 Journamic (Journamic) 2 women -///>-///////////////////////////////		Natalizumah ²⁴	74 pregnancies	Uncontrolled study	✓	√	2012
Database Number of a border of a part of a par	German MS Pregnancy	Natalizumah ²⁵	12 women				2012
NotatizemableNotat	Database			78 DM upoyposod womon	<u> </u>	•	2014
Interface Description Description Control Control <thcontrol< th=""> Control Control</thcontrol<>		Natalizumab ²⁶	101 women	78 DM unexposed women	\checkmark	\checkmark	2015
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bit is? 32 men 75 Mit metsposed women *		D. 1.7 27		41 DM Interferon-B exposed women			
Interferon # Image and the sector #		DMTs ²⁷	32 men	75 DM unexposed women	\checkmark	✓	2010
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	Database from 16 hospitals,	DMTs ⁵⁴	34 pregnancies	54 DM unexposed pregnancies	~	~	2007



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) therapyspecific 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

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	✓	✓	\checkmark		
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	✓	✓	\checkmark		
Systematic data collection	✓	✓	\checkmark		
Limitations					
Small study size	✓	✓	\checkmark		✓
Long study period	✓	✓	✓		
Early outcomes likely underreported	✓	✓	\checkmark		
Volunteer bias	✓	✓	✓		
Loss to follow-up	✓	✓	✓		
Reliance on patient-reported data	\checkmark	\checkmark	\checkmark		
Can be resource intensive	\checkmark	\checkmark	\checkmark		\checkmark
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

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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> The power of **knowledge**. The value of **understanding**.

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