Existing Databases Useful for Pregnancy Exposure and Fetal Outcomes Research: Case Study in Multiple Sclerosis

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DISCLOSURES

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BACKGROUND

- If the target population for a new drug includes women of child-bearing potential or if concerns for use during pregnancy emerged, regulatory agencies require that pharmaceutical companies investigate the drug's safety during pregnancy in the postauthorization phase.
  - Regulatory agencies often request prospective postauthorization pregnancy exposure registries.
  - However, retrospective studies using population-based registries and health care databases have been shown to be valuable for evaluating drug safety in pregnancy.[1-4]
- Certain data source capabilities are needed to evaluate medication exposure in pregnancy and fetal/infant outcomes:
  - Accurate measurement of medication exposure and timing of exposure during pregnancy
  - Early identification of pregnancies if evaluating spontaneous abortions and/or terminations
  - Linkage of mothers and offspring
  - Accurate ascertainment of outcomes
  - Ability to follow offspring for some time after delivery to identify adverse outcomes not obvious at birth
  - Availability of an appropriate comparison or reference population within the data source
  - Inclusion of a sufficient number of pregnancies to generate outcome measures with appropriate statistical precision
- For multiple sclerosis (MS), existing postauthorization pregnancy safety studies are most commonly prospective, treatment-specific registries.
  - These and other targeted pregnancy safety studies in patients with MS have mostly failed to deliver timely and robust information, even many years after initial marketing authorization, due to small study populations, lack of an internal comparison group (disease matched and/or healthy populations), long study durations due to slow enrollment, and lack of long-term follow-up of offspring, including developmental progress.
  - Existing health care databases have rarely been used in pregnancy safety studies of MS treatments.

OBJECTIVES

1. Evaluate the strengths and limitations of existing data sources, including population-based registries and health care databases, that could be used to evaluate risks to mother and infant associated with use of medications during pregnancy.
2. Assess the feasibility of conducting a database study to evaluate these risks in women exposed to intravenous MS-specific medications during pregnancy.

METHODS

- Information was abstracted from articles published since the year 2000 that used population-based registries or existing health care databases to examine the association of maternal drug exposure with the risk of congenital malformations.
- For identified data sources that had access to information on biologics administered by specialists, we contacted data custodians to evaluate the feasibility to assess the risk of adverse outcomes in women exposed to intravenous disease-modifying therapies (DMTs) during pregnancy.

RESULTS

Objective 1: Pregnancy Safety Studies Using Existing Databases

- 21 data sources identified in the literature were capable of mother-offspring record linkage with access to data on maternal medication exposure and congenital malformations (Table 1):
  - 10 health care claims databases
  - 7 medical records databases
  - 4 population-based national registries
- All data sources included information on medication dispensing or prescribing, with the associated date, which can be used to estimate the gestational timing of the exposure.
- Some data sources did not identify all pregnancies at an early stage and therefore could not capture all early pregnancy losses.
- Access to health records for validation (a key feature for some of the infant outcomes) was possible for the majority of these data sources (81%).
- As long as individuals maintain care through their provider (in the case of 7 data sources using medical records) or their insurance company (10 data sources using claims data), their records were available and allow infant follow-up for 1 year after birth. For the national registries, 1-year follow-up was available for all offspring.

Objective 2: Databases for the Study of Pregnancy and Infant Outcomes in Women With MS

- From the 21 identified data sources, 13 were considered viable options for conducting pregnancy safety studies among women with MS (Table 2):
  - 6 health care claims databases
  - 4 medical records databases
  - 3 population-based national registries
- Characteristics of the selected data sources included the following:
  - Large sample size
  - Potential to study intravenous DMT exposures
  - Able to estimate the gestational timing of exposure
  - Able to identify infant outcomes for 1 year after birth
  - Information readily available on potential comparators
- 11 of the 13 data sources could validate outcomes:
  - 9 data sources used medical record review
  - 2 data sources used medical record review and registry data

Table 1. Summary of Data Sources

Data Source	Primary Data Source	Source Population	Coding[a]	Year Drug Data First Available	Outcome Validation Possible	Source of Medication Information[b]	Medication Information Available[c]
HIRD US	**Claims data**	**Commercially insured individuals**	**ICD-9**	**2006**	**Yes**	**Pharmacy dispensing, outpatient**	**Yes**
MarketScan US	**Claims data**	**Commercially insured individuals**	**ICD-9 ICD-10**	**1995**	**No**	**Pharmacy dispensing, inpatient[d] and outpatient**	**Yes**
Medicaid US	**Claims data**	**Low-income beneficiaries**	**ICD-9**	**Unknown**	**Yes**	**Pharmacy dispensing, outpatient**	**Unknown**
STORK, Optum US	**Claims data**	**Commercially insured individuals**	**ICD-9**	**1994**	**Yes**	**Pharmacy dispensing, outpatient**	**Yes**
Military Health System US	Medical records from direct care; claims data from civilian care	Active duty and retired service members and their families	ICD-9	Unknown	Yes	Pharmacy dispensing, outpatient	Unknown
Kaiser Permanente, N. California US	**Medical records**	**Commercially insured individuals residing in N. California**	**ICD-9**	**1998**	**Yes**	**Pharmacy dispensing, outpatient**	**Yes**
Kaiser Permanente S. California US	**Medical records**	**Commercially insured individuals residing in S. California**	**ICD-9**	**1998**	**Yes**	**Pharmacy dispensing, outpatient**	**Yes**
TennCare US	**Medical records**	**Low-income beneficiaries residing in Tennessee**	**ICD-9**	**1985**	**Yes**	**Pharmacy dispensing, outpatient**	**Unknown**
British Columbia Canada	Claims data	Residents of British Columbia	ICD-9	1993	Yes	Pharmacy dispensing, outpatient	Unknown
Québec Canada	**Claims data**	**Residents of Québec Province**	**ICD-9 ICD-10**	**1997 (1980 for elderly and recipients of social welfare)**	**Yes**	**Pharmacy dispensing, outpatient**	**Yes**
Western Australia Australia	Claims data	Residents of Western Australia	ICD-9 ICD-10	1948 for a limited population	Yes	Pharmacy dispensing, outpatient, private hospitals	Yes
ÉFEMÉRIS France	Claims data	Residents of Haute-Garonne who fill prescriptions	ICD-10	2004	No	Pharmacy dispensing, outpatient	Unknown
GePaRD Germany	**Claims data**	**Insured persons from four statutory health insurance providers**	**ICD-10**	**2004**	**No**	**Pharmacy dispensing, outpatient**	**Yes**
Emilia-Romagna Italy	Claims data	Residents of the Emilia-Romagna region	ICD-9	2003	No	Pharmacy dispensing, outpatient	Yes
Denmark	**National registries**	**Danish citizens**	**ICD-8 ICD-10**	**1995 or 1998**	**Yes**	**Pharmacy dispensing, outpatient**	**Yes**
Finland	National registries	Permanent residents of Finland	ICD-9 ICD-10	1994-95	Yes	Pharmacy dispensing, outpatient	Yes
Norway	**National registries**	**Residents of Norway**	**ICD-10**	**2004**	**Yes**	**Pharmacy dispensing, outpatient**	**Yes**
Sweden	**National registries**	**Residents of Sweden**	**ICD-10**	**1994**	**Yes**	**PDR: pharmacy, outpatient; MBR: patient-reported**	**Yes**
CPRD UK	Medical records	General practice patients in the UK	Read codes	1987	Yes	Prescriptions in electronic medical records	Yes
THIN UK	Medical records	General practice patients in the UK	Read codes	2003	Yes	Prescriptions in electronic medical records	Yes
MEMO UK (Scotland)	**Medical records**	**Residents of the Tayside region**	**ICD-9 ICD-10**	**1993 (1989 for a limited set of drugs)**	**Yes**	**Pharmacy, outpatient**	**Yes**

CPRD = Clinical Practice Research Datalink; ÉFEMÉRIS = Évaluation chez la Femme Enceinte des Médicaments et de leurs Risques; GePaRD = German Pharmacoepidemiological Research Database; HIRD = HealthCore Integrated Research Database; ICD = International Classification of Diseases; MBR = medical birth register; MEMO = The Medicines Monitoring Unit; PDR = Swedish Prescribed Drug Register; STORK = Systematic Tracking of Real Kids; THIN = The Health Improvement Network; UK = United Kingdom; US = United States.

Bolded rows indicate the 13 data sources selected as feasible options for conducting pregnancy safety studies among women with MS (see Table 2).

[a] The deadline for the US to begin using the International Classification of Diseases, 10th Edition, Clinical Modification (ICD-10-CM) in clinical practice for diagnosis coding and the Procedure Coding System (ICD-10-PCS) for inpatient hospital procedure coding was October 1, 2015. This table presents the coding system(s) used in the selected published reports, which is based on what data were available at the time research was conducted. The coding system for future research will depend on data lag times.

[b] Medical claims include drugs administered via inpatient or outpatient settings through specific procedures (e.g., infusion) for which a procedure code exists.

[c] Information includes dosing frequency, days' supply, quantity dispensed, etc.

[d] Inpatient dispensings are available for a small subpopulation via the Hospital Drug Database.

Table 2. Information on Potential Data Sources Suitable to Study Pregnancy and Infant Outcomes Among Women Exposed to MS Treatments

Data Source Country	Data Lag/ Time to Data Completion	Patients' Duration in Database[a]	Number of Women Aged 15-45 Years With MS (Timeframe)
HIRD US	6 months	~3 years	31,295 (Jan 2006-Apr 2016)
MarketScan US	~6 months; depends on data type	Mean: 2.6 years for mothers, 2.7 years for fathers, 2.5 years for offspring	25,729 (2014)
Medicaid US	18 months	Unknown	Estimated: ~23,819 (2011)[b]
STORK, Optum US	6-9 months	~2.5 years	7,421 (2015)
Kaiser Permanente, N. California, US	A few weeks	Unknown	1,200 (2015)
Kaiser Permanente, S. California, US	1 year	Mean: 9.5 years for mothers, 11 years for fathers, 5 years for 70% of offspring	1,395 (2015)[c]
TennCare US	6 months to 1 year	43 months for mothers, 63 months for offspring (fathers not assessed)	976 (2013)
Québec Canada	12 months	Maximum: 17 years for mothers and offspring; no follow-up of fathers	491 (2015)
GePaRD Germany	~2 years	Unknown	Unknown
Denmark	Variable, depends on data	During a patient's residence in Denmark	Unknown
Norway	4-5 months	During a patient's residence in Norway	~2,000
Sweden	Not applicable[d]	During a patient's residence in Sweden	Unknown
MEMO UK (Scotland)	6 months to 1 year	Until a patient's death or censorship	Scotland: 2,580; Tayside: ~300 (to June 2015)

[a] The questionnaire asked what is the average amount of time (in months or years) that adult mothers, adult fathers, and offspring remain in the database.

[b] Some data sources require collaboration with an academic institution that would analyze the data.

[c] In-house analysis means that analyses must be conducted only by the data custodian or selected academic partners.

[d] Most Swedish registries release data only once a year.

DISCUSSION

- Population-based database studies are a feasible approach to evaluate women exposed to intravenous, MS-specific medications during pregnancy and their offspring.
  - Because exposure to DMTs in pregnancy is relatively uncommon, large databases or several databases may be needed to achieve a meaningful study size within a reasonable timeframe and to accommodate one or more internal comparator groups.
- A cohort study design set within one or more existing health care databases has scientific advantages:
  - Study of multiple endpoints that can be expanded to include additional outcomes if necessary, such as specific birth defects.
  - Data captured for routine purposes, such as medical care, insurance billing, and mandatory population-based reporting, are free of research-related biases.– Multiple internal comparator groups can be utilized.
  - When data are linked with birth defect registries, completeness of ascertainment and quality of diagnosis can be assumed to be high.
  - For some national registries, follow-up is virtually lifelong.
  - Studies can include a larger number of patients in a shorter time than prospective registries, and results can be available more quickly.

CONCLUSIONS

- To obtain more meaningful data for patients and physicians, using existing health care databases and national registries to evaluate the safety of new medications among women with MS with exposure to DMTs during pregnancy should be considered.
- While we chose MS as a case study, this conclusion may also apply to other disease areas.

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