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Medication Exposure in Pregnancy Risk Evaluation Program

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Abstract

To describe a program to study medication safety in pregnancy, the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP). MEPREP is a multi-site collaborative research program developed to enable the conduct of studies of medication use and outcomes in pregnancy. Collaborators include the U.S. Food and Drug Administration and researchers at the HMO Research Network, Kaiser Permanente Northern and Southern California, and Vanderbilt University. Datasets have been created at each site linking healthcare data for women delivering an infant between January 1, 2001 and December 31, 2008 and infants born to these women. Standardized data files include maternal and infant characteristics, medication use, and medical care at 11 health plans within 9 states; birth certificate data were obtained from the state departments of public health. MEPREP currently involves more than 20 medication safety researchers and includes data for 1,221,156 children delivered to 933,917 mothers. Current studies include evaluations of the prevalence and patterns of use of specific medications and a validation study of data elements in the administrative and birth certificate data files. MEPREP can support multiple studies by providing information on a large, ethnically and geographically diverse population. This partnership combines clinical and research expertise and data resources to enable the evaluation of outcomes associated with medication use during pregnancy.

Keywords

Pregnancy; Birth outcomes; Distributed data network

Introduction

Decision-making regarding safe use of medications during pregnancy is challenging for a number of reasons. Pregnant women are generally excluded from clinical trials for ethical concerns about the drug's impact upon the developing fetus. This has resulted in the current counterproductive situation in the United States and elsewhere that little information is available about the effects of drug exposure during pregnancy on the mother or fetus at the time the drug is introduced to market. As a result, only a limited number of drugs are labeled as approved for use during pregnancy. The lack of rigorous postmarketing studies evaluating birth outcomes associated with in utero exposure to most medications is unfortunate, and limits the ability of physicians and patients to make fully informed decisions about the risks and benefits of medications during pregnancy.

The need for routine and ongoing postmarketing research and surveillance on medication use during pregnancy is well-recognized [1, 2] and has been recently highlighted by controversies related to potential risks of antidepressant use during pregnancy [3].

Furthermore, tolerance for risk of harm to pregnant women and their developing infants is very low. As a result, research on medication use during pregnancy must include evaluation of rare adverse events. Such research into the safety of medications for pregnant women requires a large diverse population, well-documented patient characteristics, unbiased assessments of both outcomes and medication use, and adequate longitudinal follow-up.

While pregnancy registries developed by university-based research groups, government agencies, and pharmaceutical companies have been created to evaluate medication-associated pregnancy outcomes, these registries have well-known limitations. The small number of women included in many registries limits their ability to identify low- to moderate-risk teratogens. Further, appropriate methods and comparison groups to evaluate the risks for pregnancy outcomes using these registries are often uncertain. Additionally, pharmaceutical company registries usually include only the drug product(s) they manufacture. While interview-based case-control studies have also been used to assess the association between medication use during pregnancy and birth outcomes, the potential for differential recall among mothers of infants with adverse birth outcomes compared to mothers of infants without adverse outcomes is a concern. In addition, this approach is inefficient when assessing a large number of outcomes, longer-term outcomes and absolute risks of outcomes.

Administrative health plan databases have also been used to evaluate medication use during pregnancy. For this use, health plan databases that contain information about drug exposures must have mothers' and infants' information linked to each other. When such mother-infant linkages are performed, health plan databases offer several advantages over other approaches. For example, exposures and birth outcomes of large numbers of women are accessible. In addition, rather than focusing on one specific drug or disease state, information is available on all prescription medications dispensed, enabling studies on a wide range of medications. Because the data on medication use are collected from pharmacy databases independent from mother or infant outcomes, such data are not subject to biases that can arise from parental recall. Congenital anomalies, adverse perinatal outcomes and long-term outcomes can all be evaluated. Linkage to birth certificate data, in addition to other medical record and laboratory data, can provide additional information not readily available in the administrative databases.

Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP)

In 2009, the U.S. Food and Drug Administration (FDA) announced the creation of the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP). This pilot program is intended to provide a large, ethnically and geographically diverse population with which to address a variety of important and timely issues surrounding the safety of medication use during pregnancy. As such, MEPREP is intended to provide an ongoing avenue for research.

MEPREP is a collaborative effort between FDA and researchers at the HMO Research Network (HMORN), Kaiser Permanente Northern and Southern California, and Vanderbilt University School of Medicine. In MEPREP, all participating organizations link administrative health plan data with additional data sources. Necessary data linkages have been developed at each of the participating sites to enable multiple studies of birth outcomes associated with in utero exposure to medications. Current program components include maternal-infant record linkage of all women delivering an infant between January 1, 2001 and December 31, 2008, and linkage to birth certificate data for infants. The aim of MEPREP is not to provide a large database for data-mining, but to provide the expertise and

data resources to enable studying drug exposures for which there is a signal of potential fetal risk from animal studies, human case reports, or other published literature.

In this paper, we describe the organizational structure and data resources of MEPREP.

Organizational Model

Participating Health Systems and Research Centers

MEPREP brings together the clinical and research expertise and population-based databases from three FDA contract sites (research centers) which conduct postmarketing surveillance studies in collaboration with FDA: the HMORN, Vanderbilt University School of Medicine/Tennessee State Medicaid, and Kaiser Permanente of California. Encompassed within these three contract sites are 11 health plan-affiliated research units, including Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Georgia, Kaiser Permanente Northwest, Kaiser Permanente Colorado, Harvard Pilgrim Health Care Institute, Group Health Research Institute, HealthPartners Research Foundation, Lovelace Clinic Foundation, the Meyers Primary Care Institute/Fallon Community Health Plan, and Vanderbilt University School of Medicine. The population-based databases of the health plans include diverse populations with a broad age range for a wide array of medical care delivery models (Table 1). The proportion of Medicaid beneficiaries ranges from <1 to 100% of the included populations. Overall, the health plans have nearly 12 million current enrollees within nine states, representing approximately 4% of the U.S. population.

The institutional review boards (IRBs) of all participating organizations (and the state departments of public health, where applicable) have approved current MEPREP studies and program activities.

Sources of Data

The data resources for MEPREP include information on maternal and infant characteristics and medical care from the automated databases of the 11 health plans associated with the three FDA contract sites and birth certificate data obtained from the state departments of public health. The data sources used to build the program allow access to patient level health care information for populations with broad age, sex, geographic, racial and ethnic diversity. Since available data are from sources composed of defined populations, outpatient prescription medication exposures and health care encounters from a variety of settings (e.g., ambulatory and emergency department visits, and inpatient care) are captured and can be uniquely linked for each individual. Each health plan has enrollment, demographic, diagnoses, procedures (including laboratory tests performed), and pharmacy dispensing data. All study sites have previously collaborated in multi-site studies.

MEPREP Program Structure

The program structure consists of the Steering Committee, Coordinating Center, Technical Working Group, and the Investigator Groups. Ad hoc subcommittees and working groups are engaged as needed.

The MEPREP Steering Committee has primary responsibility for leadership of MEPREP and oversight of program activities. The Steering Committee consists of representatives from the research centers/contract sites and from FDA, ensuring that investigators from both FDA and contract sites have input into MEPREP priorities and activities.

The HMORN Coordinating Center at Harvard Pilgrim Health Care Institute serves as the MEPREP Coordinating Center, and is responsible for facilitating and organizing all program

activities, and for providing expertise on study design, statistical analysis, data processing, and data management activities.

The Technical Working Group is responsible for completion of specific program-related tasks. The Technical Working Group includes investigators from FDA and study sites, as well as site programmers and support staff. Select specific tasks include the development of data file specifications and the determination of data elements for validation through medical chart reviews.

For each study, an Investigator Group is formed; the Investigator Group represents all of the operational units participating in a particular study and is responsible for maintaining and following a study protocol that is specific, practical, and well-documented. Members include the Principal Investigators (PI) at sites contributing data to a study question and representatives of FDA. MEPREP currently involves more than 20 FDA and site medication safety researchers within these Investigator Groups for ongoing descriptive and pilot projects.

Data Development Across Sites

The Coordinating Center and the Technical Working Group lead data development across the sites, including ongoing documentation specifying the data extraction process (identification of mothers/deliveries and infants, mother and infant linkage methods, and creation of unique patient identifiers), data file specifications, and site-specific issues related to dataset creation. This data development process entails defining common variable names, labels, codes, and definitions.

MEPREP operates as a distributed research network [4, 5]. Rather than creating a large, centralized database, datasets linking healthcare data for mothers and infants are maintained at each site. The health plans have different source data systems. Transformation of the source data into standard files with the same data structure and variable names across all sites enables more efficient querying of the data and quality checks. MEPREP currently contains standardized data files for enrollment, demographic characteristics, inpatient and outpatient utilization, diagnoses and procedures, and outpatient pharmacy dispensings from health plan administrative data for both mothers and infants, and birth certificate data obtained through the state departments of public health (Table 2). The linkage of the birth certificate data to the administrative health plan data provides information about additional clinical and demographic information including known confounders (e.g., parity, smoking status). Cohorts of women delivering an infant between 2001 and 2008 have been identified using the automated administrative databases at the 11 health plans. Infants born to these women have been identified through maternal-infant databases maintained at the sites (pregnancy registries or liveborn registries) and through unique family identification numbers included in the health plan enrollment data, name/address/birthdate linkages using health plan data, and/or linkage with birth certificate data obtained from the state department of public health. Health plan identification numbers are replaced with project-specific, randomly-generated identification numbers for both mothers and infants. Related offspring are identifiable through linkage to the mother's identification number, which allows correlated data to be taken into account in analyses. Core MEPREP datasets developed at all sites are described in Table 2.

For specific studies, computer analytic programs, for instance written using SAS software (SAS Institute, Inc., www.sas.com), are developed at the coordinating center or lead project site and executed at each site to identify study subjects and generate study-specific data elements. For descriptive studies in which the reportable results are aggregate data, site-specific tables can be generated by standard programs from source data at each site and then

combined at the lead site to support the final analyses; there is no need in such studies to transfer person-level data. When there is a compelling need to generate a combined data set with person-level data for complex statistical analyses, only the minimum data necessary to support analyses are sent to the lead site for final analysis.

At all sites, electronic medical records (EMRs) or non-automated hard copy medical records are available to research personnel for review either in the on-site research facilities, in clinicians' offices, or in hospitals, subject to IRB oversight and applicable federal, state, and other regulation. These records can capture vital signs, diagnoses, providers' notes, smoking status, results of laboratory tests, diagnostic imaging procedures, and other tests, such as pathology analyses. Medical record reviews are performed by trained personnel in each health plan for research and for quality assurance reporting.

Current MEPREP Activities

MEPREP data currently include information on 1,221,156 children delivered to 933,917 mothers during the period 2001–2008. Overall, 11% of mothers were <20 years of age and 15% were ≥35 years of age on the date of delivery. The distribution of maternal age at birth is comparable to the distribution for the U.S. population during 2005. [6].

Several descriptive studies are currently being conducted using MEPREP, including evaluations of the prevalence of use of anticonvulsant, antidiabetic, antipsychotic, antiviral, and asthma medications. We are also conducting studies to evaluate the validity of data elements within the databases and gestational age assumptions based upon administrative data.

Limitations

While the use of MEPREP administrative health plan and birth certificate data are not subject to biases that can arise from parental recall, MEPREP data sources do have limitations. As with other research that uses electronic pharmacy dispensing records to identify drug use, we cannot ascertain whether medications dispensed were ingested. Over-the-counter and inpatient medications are not consistently captured in the data. In addition, some diagnosis codes require medical chart confirmation. Finally, pregnancy outcomes other than livebirths, including spontaneous and induced abortions, are not captured at this time.

Future Directions

We hope to expand both the MEPREP data resources and research agenda, contingent upon IRB approval at the participating organizations and state departments of public health, with input from both FDA and the research centers to include other pregnancy outcomes (fetal deaths, spontaneous and induced abortions), as well as linking to other data sources, both within the health plans (e.g., laboratory test results, vital signs, and fetal ultrasound data within the EMRs) and outside of the health plans (e.g., fetal death certificates and death certificates).

In addition to the ongoing descriptive and validation studies described above, a major focus of MEPREP's research agenda may include studies of the association between in utero exposure to specific medications and congenital anomalies or other birth outcomes (e.g., preterm birth). Specific medication classes of interest to program researchers include opioids, anti-infectives (including antivirals), asthma medications, antidiabetics, antipsychotics, and antiepileptics.

Conclusion

Recent studies on the extent of medication use during pregnancy and potential for associated adverse outcomes highlight the importance of examining the effects of medications on the fetus. MEPREP enables evaluation of both birth outcomes associated with medication use during pregnancy and patterns and trends in medication use during pregnancy. The participating sites are ethnically and geographically diverse, and include a wide array of medical care delivery models. The total number of births from the combination of these sites is approximately 150,000 per year, including more than 1.2 million infants for the period 2001–2008. The linked datasets developed as part of MEPREP allow the analysis of comparable data across multiple sites and improve computer programming efficiency and accuracy. Research conducted through this partnership will provide valuable information for patients and physicians when making decisions about medication during pregnancy.

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Characteristics of the Health Care Systems Participating in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), 2007

Table 1

	TennCare	Medicaid	KPNC	KPSC	HPHC	FCHP	HPRF	KPCO	KPNW	KPGA	LCF	GHC
Total enrollment, × 1,000	1,483	3,200	3,240	805	190	620	434	487	286	240	540	
Structure %												
Staff/group health maintenance organization	0	100	100	20	53	64	100	100	90	90	80	
Independent Physician Association	0	0	0	80	46	0	0	0	10	10	20	
Preferred provider	0	0	0	0	1	36	0	0	0	0	0	
Medicaid program	100	0	0	0	0	0	0	0	0	0	0	
Member age, years (%)												
17	48	22	25	24	19	35	22	23	24	39	20	
18–4	30	35	36	39	33	28	34	34	39	25	33	
45–64	13	29	28	33	29	30	30	31	31	20	33	
65	10	13	11	4	19	4	14	13	7	15	13	
Female (%)	58	51	52	52	51	52	53	52	52	52	53	
Race (%)												
White	60	67	40	75	87	85	75	84	63	55	82	
Black/African-American	30	6	9	16	2	6	6	3	33	1	3	
Asian American	1	13	10	5	3	5	2	5	<1	1	6	
Hispanic	4	10	38	4	8	4	15	6	<1	38	1	
Native American	<1	1	<1	<1	<1	<1	1	1	<1	2	4	
Other	4	<1	2	0	0	0	1	1	4	0	3	

Abbreviations for sites/research units are as follows: *KPNC* Kaiser Permanente Northern California, *KPSC* Kaiser Permanente Southern California, *KPGA* Kaiser Permanente Georgia, *KPNW* Kaiser Permanente Northwest, *KPCO* Kaiser Permanente Colorado, *HPHC* Harvard Pilgrim Health Care Institute, *GHC* Group Health Research Institute, *HPRF* HealthPartners Research Foundation, *LCF* Lovelace Clinic Foundation, *FCHP* Meyers Primary Care Institute/Fallon Community Health Plan

Table 2

Standardized data files currently available at each Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) site

File	Source of data	Description and key data elements
Mother/infant linkage	Linkage based upon data in health plan's administrative data, pregnancy/birth registry data, and/or birth certificate data	Records of the unique, randomly generated identification number for each child along with the unique, randomly generated identification number for the mother
Demographic	Health plan administrative data	Information on the sex, date of birth, race and ethnicity for each mother and child
Enrollment	Health plan administrative data	Health plan membership information, including dates of plan enrollment, termination of membership, and drug benefit coverage
Dispensing	Health plan administrative/pharmacy or claims data	Outpatient drug dispensings, including the dispense date, National Drug Code (NDC), generic name, amount dispensed, and days of supply
Diagnosis	Health plan administrative/clinical or claims data	Diagnoses, recorded as International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM), and dates of diagnoses associated with hospitalizations or ambulatory visits identified from administrative health plan data
Procedure	Health plan administrative/clinical or claims data	Hospital and ambulatory procedures (laboratory tests, radiology examinations, surgeries, or others), coded according to International Classification of Diseases, 9th revision (ICD-9) codes, Current Procedural Terminology (CPT) codes, Health Care Financing Agency Common Procedure Coding System (HCPCS) codes and site-specific codes
Utilization	Health plan administrative/clinical or claims data	Characterizes inpatient stays, including admission and discharge dates, provider, and discharge disposition
Birth certificate	Birth certificate data from state department of public health	Data obtained from the state departments of public health including gestational age, prenatal care received, parity, gravidity, maternal smoking status, maternal and paternal age, race, and educational level achieved, congenital malformations and other perinatal outcomes, as well as additional medical and health information documented in the child's birth certificate
Crosswalk	Linkage to health plan administrative data	Links the health plan or patient identification number to the unique, randomly generated identification number that links information across the data files described above