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Linkage between the Danish National Health Service Prescription Database, the Danish Fetal Medicine Database, and other Danish registries as a tool for the study of drug safety in pregnancy

Abstract: A linked population-based database is being created in Denmark for research on drug safety during pregnancy. It combines information from the Danish National Health Service Prescription Database (with information on all prescriptions reimbursed in Denmark since 2004), the Danish Fetal Medicine Database, the Danish National Registry of Patients, and the Medical Birth Registry. The new linked database will provide validated information on malformations diagnosed both prenatally and postnatally. The cohort from 2008 to 2014 will comprise 589,000 pregnancies with information on 424,000 pregnancies resulting in live-born children, ~420,000 pregnancies undergoing prenatal ultrasound scans, 65,000 miscarriages, and 92,000 terminations. It will be updated yearly with information on ~80,000 pregnancies. The cohort will enable identification of drug exposures associated with severe malformations, not only based on malformations diagnosed after birth but also including those having led to termination of pregnancy or miscarriage. Such combined data will provide a unique source of information for research on the safety of medications used during pregnancy.

Keywords: malformations, teratology, therapeutic drug monitoring, epidemiological methods, registries

Introduction
In all, >50% of pregnant women redeem at least one prescription during pregnancy, but the fetal effects of many types of medications have not been ascertained. This paucity of information hampers management of a number of diseases during pregnancy as well as the development of new obstetric medications.

In the early 1960s, Lenz et al and McBride first described an association between the use of medication (thalidomide) during pregnancy and severe malformations. Since then, a number of teratological medications have been described. Unfortunately, sufficient information on safety during pregnancy is still lacking for many medications, in part due to methodological limitations. No existing in vitro or animal models can provide valid information on the likelihood of fetal risk. Randomized controlled trials focused on adverse fetal effects are almost always unethical. For randomized controlled trials that would be possible to conduct during pregnancy (eg, studies on discontinuation of antidepressants), huge sample sizes are needed to investigate specific malformations. Studies relying on spontaneous reports of malformations are subject to severe bias, including recall bias, and the interpretation of the findings is hampered by the fact that spontaneous report system data do not inherently include the underlying
denominator. Consequently, most information on the use of medications during pregnancy derives from epidemiological studies, whose quality relies heavily on the validity of the underlying data.

Studies on the safety of medications used during pregnancy that are based on existing epidemiological data sources have a number of limitations.1–4 First, results can be distorted by missing data on prenatally diagnosed malformations that led to miscarriage or pregnancy termination. The resulting bias would be proportional to the severity of the malformations.11 For example, phocomelia (as seen after thalidomide exposure), now often detected during prenatal screening, is associated with a high propensity for pregnancy termination.12 Thus, this malformation would be potentially undetectable using the sole data on live-born children. Second, exposure information is subject to some extent of misclassification regardless of whether it is based on self-report or administrative databases. Third, the validity of malformation diagnoses may vary according to the type and severity of the defect or sequence. Finally, no known teratogens increase the risk of all birth defects, and therefore, specific drugs need to be studied in relation to specific birth defects, requiring very large datasets. The consequences of these limitations include potentially delayed or failed detection of teratological drug effects or reporting of false-positive associations (eg, related to confounding by indication).

Here, we describe the creation of a large nationwide database, containing information on malformations diagnosed both prenatally and postnatally and linked to information on prescriptions redeemed during pregnancy.

Data linkage
Data will be linked using the unique ten-digit civil personal register (CPR) number, assigned by the Danish Civil Registration to all Danish citizens at birth or upon immigration.13 The cohort will comprise all clinically recognized pregnancies in Denmark starting in 2008 by linking the Danish National Registry of Patients (covering all Danish hospitals), the Danish Fetal Medicine Database, and the Danish Medical Birth Registry.14 Information on exposure to medications will be obtained through linkage with the Danish National Health Service Prescription Database (DNHSPD).15

The cohort from 2008 to 2014 will comprise 589,000 pregnancies with information on 424,000 pregnancies resulting in live-born children, ∼420,000 undergoing prenatal ultrasound scans, 92,000 terminations, 65,000 miscarriages, 2,000 stillborn children, and 6,000 with other outcomes (including ectopic pregnancies). Data will be updated yearly with information on ∼80,000 pregnancies.

Danish National Registry of Patients
The registry contains information on all in- and outpatient contacts in the hospital system since 1995.16 Diagnoses are coded according to the tenth revision of the International Classification of Diseases. The database includes information on spontaneous and induced abortions and on malformations diagnosed postnaturally (ie, also years after birth).

Danish Fetal Medicine Database
This nationwide clinical quality database was established both to enable quality assessment of the prenatal screening in Denmark and to provide data for research.17 Importantly, it holds information on malformations diagnosed prenatally. All departments involved in prenatal screening (such as nuchal translucency and malformation scans) provide data to this central database. The data are collected in a standardized way as all departments use the same software (Astraia, Munich, Germany) to store the data as part of everyday clinical management. The departments also use identical algorithms to collect and send the data to the central database, hosted by the Danish Regions’ Quality Assessment Unit,18 where they are linked to information from the Medical Birth Registry, the Danish National Registry of Patients, and the Danish Central Cytogenetic Registry using the CPR numbers of the mother and her offspring.

The population in the Fetal Medicine Database consists of women accepting prenatal screening or ultrasound. Data on all first trimester screenings and second trimester malformation scans are included. Between 2008 and 2012, ∼92% of the pregnant population in Denmark underwent first trimester screening (eg, 279,105 pregnancies between 2008 and 2012), and ∼96% of the pregnancies were scanned between 18 weeks and 22 weeks of gestation. In all, <1% of the pregnancies that reach 12 weeks of gestation undergo no prenatal screening. The local databases contain information such as crown-rump length, nuchal translucency thickness, method of conception, maternal characteristics (including ethnicity, weight, and smoking status), results of prenatal invasive testing (cytogenetic results), and prenatally diagnosed malformations. Importantly, information on pregnancies without prenatal screening is available through the linked Medical Birth Registry. Table 1 provides an overview of central variables in the Danish Fetal Medicine Database.
Danish Medical Birth Registry
The Danish Medical Birth Registry holds information on births in Denmark since 1973. It includes information on all stillborn and live-born children, including gestational age at birth and birth weight.

Danish National Health Service Prescription Database
The health care system in Denmark provides tax-financed partial reimbursement for most prescription medications. The entire country is served by pharmacies equipped with electronic accounting systems used primarily to secure reimbursements from the National Health Service. Each prescription is redeemed at a pharmacy, an electronic accounting system gathers this information for administration of the drug reimbursement, and the information is reported to the central registry in a standardized way. In contrast, the validity of the compliance-level information depends on the type of medication, for example, high for long-acting insulin and low for antimigraine medication. A recent study found that 30% of women who redeemed a prescription for selective serotonin reuptake inhibitors (SSRIs) during pregnancy did not report SSRI use in a written questionnaire completed during the first trimester of pregnancy, and of the women who were coded as unexposed based on the DNHSPD, 26% did report use ing and by the midwife at birth, may be subject to bias (eg, underreporting due to social norms). Thus, the use of smoking information mandates careful monitoring of potential changes during pregnancy.

The validity of the covariate data depends on the specific variables in question. For example, information on the sex of offspring is expected to be 100% valid. In contrast, information on smoking during pregnancy, which is recorded by the sonographer at the time of the first-trimester screening and by the midwife at birth, may be subject to bias (eg, underreporting due to social norms). Thus, the use of smoking information mandates careful monitoring of potential changes during pregnancy.

The validity of the outcome will depend on the completeness of the registration and the quality of the diagnoses.

Data quality

Table 1 List of central variables in the Danish Fetal Medicine Database

| Maternal characteristics | 
|--------------------------|
| CPR number               |
| Age                      |
| Ethnicity                |
| Weight                   |
| Smoking                  |
| Method of conception     |
| Pregnancy information    |
| Parity                   |
| Singleton/multiple pregancies |
| Nuchal translucency thickness |
| Prenatally diagnosed malformations |

Abbreviations: CNS, central nervous system; CPR, civil personal register number; ICD-10, International Classification of Diseases, tenth revision.

Table 2 Central variables in the Danish National Health Service Prescription Database

| Maternal characteristics | 
|--------------------------|
| CPR number               |
| Municipality and region of residence |
| Dispensing details       |
| Trade name               |
| ATC code                 |
| DDD                      |
| Date of dispensing       |

Abbreviations: ATC, Anatomical Therapeutical Chemical; CPR, civil personal register number; DDD, defined daily dose.

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One core aim of the new linked data source is to decrease the risk of selection bias due to terminations because of malformations. We expect a dramatic increase in the detection rate of severe malformations associated with a high propensity for pregnancy termination, such as anencephaly. As well, the linked data source will allow more complete registration of malformations diagnosed at birth or even months or years after birth, for example, hypospadias or atrial septal defects.

Algorithms will be constructed to estimate the consequences of potential errors in measuring the use of specific medications and prevalence of malformations based on validation studies. This will enable researchers to estimate the range of a specific teratogenic effect. For example, patients often purchase migraine medication to be prepared for future migraine attacks and, consequently, redeemed prescriptions will only lead to exposure in a certain proportion of pregnancies. This proportion may be unknown, but the discrepancy could severely bias the estimates (in general, toward the null). We will provide estimates of the consequences of the expected range of misclassifications (eg, in the case of migraine medication, if the assumption is that between 20% and 50% of the redeemed prescriptions are actually used, the algorithm will estimate the corresponding bias).

**Strengths and weaknesses**

The linked data hold an unequalled potential for comprehensive evaluation of the safety of medication used in pregnancy. The database will have a sufficiently large sample size to provide important information on many types of existing medication and will be able to address safety concerns even on newly marketed medication owing to the regular update. Because of the unique information on prenatally diagnosed malformations, it will be able to detect potential associations between medication and, eg, anencephaly that are undetectable in data on live-born children only.

The main weakness is the potential misclassification of exposure and outcome variables inherent to register based research. This is specifically true for the paramount information on medication exposure. For example, in the case of new medication, we expect no valid information on the potential noncompliance to prescriptions. This might limit the ability to detect teratogenic associations. The above-described algorithm will enable researchers to estimate the magnitude of the bias based on prior expectations of the misclassifications, but validation studies are much needed to test support expectations.

**Accessing the data**

The Department of Clinical Epidemiology at Aarhus University will maintain the new linked database for research purposes. The original data files for the Danish Fetal Medicine Database are kept by the Danish Regions’ Quality Assessment Unit, while the original data files for the DNHSPD are kept by the Department of Clinical Epidemiology at Aarhus University. The Danish Act on Processing of Personal Data permits public institutions, including universities, to retain individually identifiable health data for research purposes. Access will require permission from the Steering Group of the Danish Fetal Medicine Database. Furthermore, the use of any health data mandates project-specific permission from the Data Protection Agency (“Datatilsynet,” ). External researchers can apply for access to specific projects when the data have been validated.

For medications for which there is no direct information on the validity of using reimbursements as proxy for intake, the expected range of correspondence needs to be stated in the protocol prior to the analyses. For instance, the protocols for proposed studies on migraine medication need to address the expected low correspondence. Similarly, prior estimates of the range of validity for data on specific malformations need to be explicitly stated in the protocol.

**Conclusion**

The new linked data source will provide a unique source of information on the teratogenic potential of medications used during pregnancy.

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Disclosure

The authors report no conflicts of interest in this work.

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