Metformin use in the first trimester of pregnancy and risk of non-live birth and congenital malformations: emulating a target trial using real-world data.

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Protocol

3.C.1. Data sources. We will use two nationwide data sources for the proposed project: MAX and Truven. Both are healthcare utilization databases that record beneficiary demographic and enrollment information, as well as healthcare utilization claims including all recorded diagnoses and procedures associated with inpatient admissions and outpatient visits. They also contain claims for all filled outpatient medication prescriptions. Diagnoses are coded with the clinical modification of the International Classification of Diseases (ICD)-9 system (and ICD-10 after September 2015) and procedures with the Current Procedural Terminology (CPT)-4; both of which have been shown to have good accuracy in claims data.[149-151] The pharmacy file provides a history of drug dispensing; it records claims for each prescription fill including the date of dispensing, the drug, the quantity, the days the supply is anticipated to last, and the dose.

MAX contains information on **Medicaid beneficiaries**. We have previously published the details regarding the pregnancy cohort creation.[99] Similar information is available in Truven, a **private health insurer** that provides comprehensive medical coverage for members with active policies. Truven is the largest dataset based on commercial health insurance claims, representing more than 100 payers and 25 million covered lives annually. It is large enough to allow creation of a **nationally representative sample** of US residents with private health insurance.[145-147] Both databases are HIPAA compliant thus all patients have been anonymized. However, with appropriate permissions CMS will provide a crosswalk for patients in MAX to patient identifiers (social security numbers) that allows linkage to **electronic medical records** of women treated at hospitals within **Partners Healthcare**. In addition, Truven data contains **laboratory results** for around 10% of the beneficiaries. These data include HbA1C levels, a laboratory-based method for assessing the patient's mean blood glucose level over recent weeks. These linked cohorts allow access to highly granular patient level information (e.g., HbA1C) that will be used to inform the propensity score calibration component of the study.

3.C.2. Study Population. The study cohort will consist of pregnancies identified within both MAX and Truven data. The MAX data 2000-2013 and Truven data 2011-15 are already in house, and were used to conduct preliminary analyses. We will add any additional years as they are released. Briefly, among females age 12-50, we identify all deliveries using inpatient and outpatient delivery-related diagnostic and procedure codes from healthcare utilization claims. The deterministic linkage algorithm we have developed to accurately link mother-infant data files in MAX is based on state, Medicaid case number (which identifies family units), date of delivery, and birth hospital.[99] Several steps of data cleaning are implemented to ensure accurate linkage and avoid duplication of pregnancies.[99] Strict eligibility criteria are then implemented to ensure complete claim information. The cohort is restricted to women without restricted benefits, private insurance, or certain capitated managed care programs that underreport claims to Medicaid. We require mothers to be enrolled and eligible from at least 3 months prior to the last menstrual period (LMP) until 1 month after delivery. Infants are required to meet the same eligibility criteria as their mothers for at least 3 months following birth, unless they die before, in which case a shorter eligibility period is allowed. We have recently created a pregnancy cohort using Truven data **using the same protocol**, including performing a deterministic linkage of mother-infant data files based on insurance ID shared in families and year of birth, and imposing identical eligibility requirements.

Requirement of the maternal enrollment period prior to LMP allows for identification of prescriptions filled prior to the LMP and provides accurate ascertainment of comorbidities that pre-date pregnancy. The requirement for continuous enrollment throughout pregnancy allows for complete follow-up and complete ascertainment of drug exposures, diagnoses and procedures. Requiring enrollment of infants for at least 90 days following birth allows ascertainment of nearly all major congenital birth defects[30]. However, defects diagnosed up to 365 days after birth will be considered in sensitivity analyses. Based on these inclusion criteria, we have identified a cohort of **2,071,359** eligible mothers linked to infants in MAX (2000-2013); with the addition of data from 2014 to 2015 the cohort will be over 2.3 million. In Truven (2011-2015) the cohort now includes **904,609** eligible pregnancies; with the addition of data from 2016 to 2018 it will be around 1.5 million.

3.C.3. Study Cohort. Within a total population of **>3.5 million** publicly and commercially insured US pregnant women, we will identify a cohort of pregnancies **with pre-existing type 2 diabetes**. The definition of pre-gestational diabetes will follow a validated algorithm[152] with a positive predictive value (PPV) of 91% based on chart review. Restriction of the analyses to patients on antidiabetic therapy should further improve this PPV. After exclusion of women with gestational diabetes (648.8x or 648.0x after the first 12 weeks of gestation through delivery and no diabetes codes or antidiabetic drugs before then), the definition is based on the presence of ≥ 2 medical claims with a diagnostic code for type 2 diabetes (250.x0 or 250.x2) or 1 diagnosis for type 2 diabetes and prescriptions for non-insulin antidiabetic drugs, and ≤2 type 1 diabetes diagnosis.[153]

3.C.4. Exposure definition. We will consider the most commonly used antidiabetic agents (Table 1), with or without insulin**,** and will examine the effect of newer agents as data accumulate. However, drugs with <100 exposed pregnancies will not be presented individually but grouped within antidiabetic classes. Exposure to medications will be derived from pharmacy dispensing records. Automated pharmacy dispensing information is usually seen as the gold standard of drug exposure compared to self-reported information[78] or prescribing records in outpatient medical records.[79] Pharmacists fill prescriptions with little room for interpretations, and are reimbursed by insurers on the basis of detailed, complete, and accurate claims submitted.[154,155] Patient recall bias are absent from healthcare utilization databases since all data recording is independent of a patient's memory or agreement to participate in a research study.[149-151] It should be acknowledged that filling a prescription does not guarantee that the medication was actually taken as prescribed. However, the risk of misclassification is lower for injections and for medications prescribed to control a chronic condition (e.g., diabetes).[156]

Table 1. List of antidiabetic medications

Class	Specific agent
Insulin	All specific types
Biguanides	Metformin
Sulfonylureas	Glimepiride, Glipizide, Glyburide
SGLT2-inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin
DPP-4 inhibitors	Alogliptin, Linagliptin, Saxagliptin, Sitagliptin
GLP-1 receptor agonist	Exenatide, Liraglutide, Lixisenatide, Albiglutide, Dulaglutide
Glitazones	Pioglitazone, Rosiglitazone
Meglitinides	Nateglinide, Repaglinide

The LMP date will be defined using a validated algorithm,[157,158] which has been demonstrated to have both a high sensitivity (>96%) and specificity (>99%) for correctly classifying trimester-specific exposure status for medications used chronically.[159] The **etiologically relevant period** of exposure has been specified a priori and will vary according to the outcome of interest. For the primary analysis, a woman will be considered exposed if she received a prescription within such relevant period. The relevant window for the study of birth defects is exposure during the first trimester, the period during which organogenesis occurs. For neonatal hypoglycemia,

hyperbilirubinemia, respiratory distress and NICU admission the relevant window is defined as exposure in the 3 months prior to delivery. For the outcomes of preterm delivery, macrosomia, shoulder dystocia, small for gestational age and preeclampsia, glycemic control and/or direct effects of the medication may be relevant during either early or late pregnancy (or both) and therefore each of these windows will be explored (i.e., LMP to day 140 of pregnancy and after day 141 of pregnancy to delivery). Analyses of late pregnancy exposure will account for the differential exposure opportunity in pregnancies resulting in preterm delivery.[160]

3.C.5. Reference group (Aims 2-3). Some women come into pregnancy controlled with oral antidiabetic agents and the question is whether to (1) switch to insulin alone, (2) stay on specific oral agents, or (3) add insulin to oral agents. Others come into pregnancy controlled with insulin and the question is whether to add metformin, or other oral agent, or to increase insulin dose in cases of severe hyperglycemia. To answer these questions, our primary reference group will consist of women with one or more prescriptions for **insulin** during the exposure window, and no prescription filling claim for any other antidiabetic agent. We will compare users of specific oral agents alone versus insulin alone. We will also assess the effects of combination therapy of insulin with metformin (aim 2) or other antidiabetic agents (aim 3) versus insulin alone. The secondary reference group for aim 3 will be women on **metformin** since women treated with insulin may have more severe diabetes; i.e., we will compare other oral agents to metformin stratifying on insulin. It is expected that some women will add insulin or metformin in combination with other antidiabetic agents; we will therefore also compare different **augmentation** strategies to a reference of continuers.

3.C.6. Outcomes (Aims 2-3) will be defined using previously validated algorithms based on inpatient and/or outpatient diagnoses and procedure claims. We have already completed a large-scale validation study involving chart review designed to optimize the accuracy of algorithms for identifying obstetric and fetal outcomes through diagnostic codes in claims data. In these studies, our claims based definitions resulted in high PPV for the outcomes of interest: cardiac malformations (77.6%), preeclampsia (94.5%), small for gestational age (86.8%), cesarean delivery (98.7%), induction (96.6%) or preterm delivery (74.5 %).[103,161] We are currently validating central nervous system defects as part of another project. Informed by these PPVs, we will conduct probabilistic bias analyses to assess the impact of misclassification on risk estimates,[162] as we have done in our prior work[82,86].

*3.C.6.a. Major malformations***.** A major malformation is defined as a structural abnormality with surgical, medical, or cosmetic importance.[163] We will follow child development from prenatal screening in maternal claims to 90 days after delivery. In sensitivity analyses we will expand the follow up to 365 days post-birth (although most major malformations will be diagnosed within weeks of delivery)[164,165]. The timeframe for diagnosis will be identical in the exposed and the reference group. Specific malformations will be identified using algorithms based on ICD-9/10-CM diagnostic codes and, when relevant, procedure codes for corrective surgery, in infant encounter claims (i.e., birth hospital discharge or subsequent infant hospitalization) and mother's claims for codes indicating a birth defect around the child's date of birth (e.g., in obstetric claims).[166] Chromosomal or Mendelian-inherited anomalies will be excluded under the assumption that the etiologies of these malformations cannot be attributable to antidiabetic agents. Birth defects will be grouped following the recommendations from the CDC National Birth Defects Prevention Study.[166] We will study **malformations overall, cardiac anomalies and central nervous system anomalies** as primary outcomes since these groups are the most common in infants born to women with diabetes. While a single claim code for a malformation is generally inadequate to accurately define the presence of a malformation, prior work from our group demonstrates that major malformations can be accurately defined based on algorithms that combine diagnostic and procedure codes (e.g., multiple diagnostic codes on different days for a specific malformation or a single code plus either a corrective surgery or infant death).[103] Additionally, we have shown that well known prenatal exposure/birth defect associations can be identified using claims data with birth defects defined base on these algorithms (e.g., diabetes and birth defects,[82] lithium and cardiac defects,[87] topiramate and oral clefts[108]), which indirectly validates the accuracy of the diagnoses.

3.C.7. Covariate assessment. Information on covariates considered for confounding adjustment are obtained from eligibility files, inpatient and/or outpatient claims for diagnoses and procedures and pharmacy dispensing records during the 3-month baseline period before LMP. We will consider seven groups of covariates that could potentially confound or modify the association between specific antidiabetic treatment strategies and the outcomes of interest in women with type 2 diabetes. The included covariates have been selected because they are potential risk factors for the study outcomes or potential proxies for such risk factors:

- **Indication**: We will consider proxies for diabetes severity (e.g., diabetes complications, hypoglycemia, hospitalizations for glucose control). **HbA1C levels** will be available in the sub-cohort with laboratory data

(Truven) and linked medical records (MAX). It is recommended to monitor HbA1C levels between monthly[48] to once per trimester[2] in pregnancy. HbA1C levels generally reflect a person's blood glucose concentration over the prior 12 weeks; although in pregnancy it can reflect the prior 4-8 weeks due to increased red blood cell turnover.[32] The recommended target HbA1C level is 6 to 6.5% in early pregnancy and <6% as pregnancy progresses.[48] However, since lower levels are associated with episodes of hypoglycemia, the target is often relaxed to <7% in clinical practice. Therefore, we will define poor control as at least one HbA1C≥ 7% in the three months preceding LMP, since those tests would affect treatment decisions early in pregnancy, and in the first trimester, since those tests would reflect glycemic control around conception, which was the strongest predictor for structural malformations in prior work.

- **Microvascular diabetes complications** including nephropathy, neuropathy, and retinopathy.[171]
- **Other comorbid conditions**: Obesity, hypertension, hyperlipidemia, PCOS, infections, hypothyroidism, hyperthyroidism, depression, as well as comorbidity score specific to pregnancy.[172]
- **Medications:** Antihypertensives, statins, weight loss medications, antidepressants, prenatal vitamins or folic acid, suspected teratogenic medications (e.g., angiotensin converting enzyme inhibitor); and number of distinct prescription drugs used, excluding antidiabetic agents, as a general marker of comorbidity.[173]
- **Maternal demographic and lifestyle** characteristics: Year of delivery, State, race, age, smoking, alcohol and illicit drug use.
- **Health care utilization**: Number of outpatient visits, hospitalizations, ultrasounds and other prenatal tests.
- **Obstetric factors**: Infertility treatment, multifetal gestation, parity, and infant sex. **We will evaluate effect modification for all outcomes by infant sex**. Secondary analyses will restrict to singletons.

While the data sources that will be employed have rich information on a wide range of potential confounders, some covariates of interest are either not coded or imperfectly recorded in healthcare utilization databases (e.g. BMI, frequency of smoking). However, we will adjust for these factors when recorded (e.g., obesity or smoking). Further, we will perform several sensitivity analyses to address the issue of potential residual confounding, including propensity score calibration based on data from the linked Partners cohort, and quantification of the impact of unmeasured confounders in sensitivity analyses.

3.C.8. Comparative safety of antidiabetic agents. The same analytic approach will be followed for each outcome, unless otherwise noted. The exposure window definition will vary for specific outcome of interest. Absolute risks, risk differences and relative risks with confidence intervals will be presented graphically when appropriate. We will provide risk estimates **for women with and without pre-gestational diabetes** and, within women with diabetes, for **treated and untreated** groups to quantify the risk conferred by the indication of diabetes**.** Then, main results will be presented for two levels of adjustment: First, as crude estimates using a cohort of women with type 2 diabetes and an active comparator to control for the potential effect of the underlying illness or factors associated with it. Second, using propensity score (**PS) stratification** to further control for proxies of diabetes severity and other potential confounders.[174] The PS will be derived from the predicted probability of treatment estimated in a logistic regression model of exposure, which will contain all covariates above without additional variable selection.[175] In case of model convergence problems, we will use lasso regression to aid with variable selection.[176] Non-overlapping areas of the PS distributions for the exposed and reference groups will be trimmed.[177] We will create 50 PS-strata based on the distribution among the exposed. The goal is to attain balance in important risk factors between the exposed and the reference groups. In the outcome models, adjusted relative risks and 95% confidence intervals will be estimated using generalized linear models (SAS PROC GENMOD with a weight statement and log link function for relative risks and identity link function for risk differences). Balance will be assessed using the standardized mean difference. An absolute standardized difference greater than 0.1 will be considered an indicator for substantial imbalances between exposure groups.[178] If imbalances remain, these covariates will be included directly in the outcome model along with weighting on the PS strata. We will assess whether diabetes severity is measured effectively by these proxies by confirming **balance in HbA1c** between exposure groups within PS strata in the subsample of subjects with laboratory data. The potential residual imbalance in glycemic control would be corrected with PS calibration (3.C.10). Generalized estimating equations **(GEE)** will be used to account for **clusters of pregnancies within mothers**, i.e., robust variances will correct for the possible correlation between multiple pregnancies of the same women during the study period.[179,180] The proportion of women with ≥2 pregnancies in currently 17% in MAX and 14% in Truven.

We will conduct and present the analyses in parallel within MAX and Truven and then pool the estimates using meta-analytic techniques that weight relative estimates by amount of information.[181,182] We will assess between-study heterogeneity, and conduct a fixed-effects (Mantel-Haenszel) or random-effects (DerSimonian

and Laird) meta-analysis as appropriate. It has been shown how PS-stratified analysis within centers followed by meta-analysis produce results that are highly comparable with the results from a pooled individual-level data analysis.[183] This approach is very different from a meta-analysis based on literature review, since results are pooled from **homogeneous study designs standardized** across data sources.

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