

Supplemental Online Content

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eAppendix 1. Information on Study Databases

eAppendix 2. Identification of Outcome Events

eAppendix 3. Diagnosis and Procedure Codes Used to Define Outcomes

eAppendix 4. Exposure Ascertainment Methodology

This supplemental material has been provided by the authors to give readers additional information about their work.

EAPPENDIX 1: INFORMATION ON STUDY DATABASES

| Site | Databases | | | | |
|--|---|-----------------------------------|--|---|---|
| | Population | Drug data and dispensing captured | Prescription drug claims | Hospitalization data | Outpatient billing data |
| British Columbia | All (excludes ~4% of population which is federally insured) | Dispensing (All) | Healthideas Database: PharmaNet Claims History extract | Healthideas Database: Extract of CIHI Discharge Abstracts ICD-9: 1994-2002; ICD-10: Since 2002 | Healthideas Database: Medical services plan fee for service billings (ICD-9) |
| Alberta | ≥18 years | Dispensing (Public) | Pharmaceutical Information Network Dispenses | CIHI Discharge Abstract Database ICD-9: 1994-2002; ICD-10: Since 2002 | Practitioner Claims (ICD-9) |
| Saskatchewan | All | Dispensing (Public) | Prescription Drug Plan Historical Claims | CIHI Discharge Abstract Database ICD-9: Until Mar 2002; ICD-10 Since Apr 2002: | Medical Services Branch (ICD-9) |
| Manitoba | All | Dispensing (All) | Drug Program Information Network (DPIN) | Hospital Abstracts User Manual Database (prior to April 1, 2004) Discharge abstract data/Manitoba Abstract Data Elements Database (since April 1, 2004) ICD-9: Apr 1979 to Mar 2004 ICD-10: Since Apr 2004 | Manitoba Health Medical- Physician Services (ICD-9) |
| Ontario | Social assistance recipients | Dispensing (Public) | Ontario Drug Benefit Plan Database | CIHI Discharge Abstract Database ICD-9: Until Mar 2002; ICD-10: Since Apr 2002 | Ontario Health Insurance Plan (OHIP) Claims History Database (Modified ICD-8) |
| CPRD | All | Dispensing (All) | General practitioner practice records linked to Hospital Episode Statistics hospitalization data and Office for National Statistics vital statistics information | | |
| IBM MarketScan® Commercial database | Commercial Database: CCAET files. Enrollment data from large employers and health plans | Dispensing (Insured) | Commercial Database: CCAED files (Jan 2006 – Dec 2016) | Commercial Database: CCAEI files (Jan 2006 – Dec 2016) | Commercial Database: CCAEO files (Jan 2006 – Dec 2016) |

EAPPENDIX 2: IDENTIFICATION OF OUTCOME EVENTS

The table below provides information on the eligible windows during pregnancy and exposure in which events were counted in the analyses of primary and secondary outcomes. Note: the term COHORTENTRY_GA was the gestational age (GA) in days when a study or comparator drug is first initiated, and OUTCOME_GA was gestational age on the date the outcome event occurred. These terms were not used in the manuscript text.

Table: Event Eligibility Windows

| Event Type | Eligible Window for Event | Event Date |
|---|---|------------------------|
| Primary Outcome | | |
| Fetal Death (stillbirth or spontaneous abortion) | \geq COHORTENTRY_GA, until and including the OUTCOME_GA (gestational age in days on the OUTCOMEDT + 1 day | Date of event or birth |
| Secondary Outcomes | | |
| Stillbirth | \geq COHORTENTRY_GA, until and including the OUTCOME_GA | Date of birth |
| Spontaneous Abortion | \geq COHORTENTRY_GA, until COHORTENTRYDT + 140 days, inclusive. | Date of event |
| Major Congenital Malformation | $>$ COHORTENTRYDT | Date of birth |

EAPPENDIX 3: DIAGNOSIS AND PROCEDURE CODES USED TO DEFINE OUTCOMES

The following diagnostic, procedure and fee codes were used to identify outcome events. An 'x' denotes all codes with the stated prefix.

Stillbirth

ICD-9 Codes

| ICD-9 Code | Description |
|-------------------|--|
| V27.1x | Outcome of delivery, single stillborn |
| V27.4x | Outcome of delivery, twins, both stillborn |
| V27.7x | Outcome of delivery, other multiple birth, all stillborn |
| 656.4 | Intrauterine death, late |

ICD-10-CA Equivalent Codes

| ICD-10-CA | Description |
|------------------|--------------------------|
| O36.4 | Intrauterine death, late |
| Z37.1x | Single stillbirth |
| Z37.4x | Twins both stillborn |
| Z37.7x | Multiples, all stillborn |

Fee-for-Service Codes (in Saskatchewan, adapted for each province)

| FFS Codes | Description |
|------------------|--------------------|
| 241P | Stillbirth |

Spontaneous Abortion

ICD-9 Codes

| ICD-9 Codes | Description |
|--------------------|---------------------------------------|
| 634.x | Spontaneous Abortion |
| 630.x | Hydatidiform mole |
| 631.x | Other abnormal products of conception |
| 632.x | Missed abortion |
| 633.x | Ectopic pregnancy |
| 637.x | Unspecified abortion |

ICD-10-CA Equivalent Codes

| ICD-10-CA | Description |
|------------------|---------------------------------------|
| O03.x | Spontaneous Abortion |
| O01.x | Hydatidiform mole |
| O02.x | Other abnormal products of conception |
| O05.x | Other abortion |
| O00.x | Ectopic pregnancy |

Fee-for-Service Codes (in Saskatchewan, adapted for each province)

| FFS Codes | Description |
|------------------|---------------------------|
| 350P | Spontaneous abortion |
| 48P, 248P | Ectopic gestation removal |

Induced Abortion

ICD-9 Codes

| ICD-9 Code | Description |
|-------------------|--------------------------|
| 635.x | Legally induced abortion |
| 636.x | Illegal abortion |

ICD-10-CA Equivalent Codes

| ICD-10-CA | Description |
|------------------|--------------------|
| O04.x | Medical abortion |

Fee-for-Service Codes (in Saskatchewan, adapted for each province)

| FFS Codes | Description |
|------------------|------------------------------|
| 50P | Therapeutic/Medical abortion |
| 250P | Therapeutic/Medical abortion |

Termination of Pregnancy for Fetal Anomaly (TOPFA, included with induced abortions in the analysis)

TOPFFA included a code for induced abortion, co-occurring with one (or more) of the following during the same care episode (i.e., hospitalization or service date) as the induced abortion code:

1. ICD-9 code 655.x or ICD-10 code O35.x
2. Livebirth
3. Stillbirth

Live birth

ICD-9 Codes

| ICD-9 Code | Description |
|-------------------|-------------------------------------|
| V27.0x | SINGLE LIVE BIRTH |
| V27.2x | TWINS, BOTH LIVE BORN |
| V27.5x | OTHER MULTIPLE BIRTH, ALL LIVE BORN |

ICD-10-CA Equivalent Codes

| ICD-10-CA | Description |
|------------------|-------------------------------------|
| Z37.0x | SINGLE LIVE BIRTH |
| Z37.2x | TWINS, BOTH LIVE BORN |
| Z37.5x | OTHER MULTIPLE BIRTH, ALL LIVE BORN |

Birth Type Mixed or Unspecified

ICD-9 Codes

| ICD-9 Code | Description |
|-------------------|--|
| V27.3x | TWINS, ONE LIVE BORN AND ONE STILLBORN |
| V27.6x | OTHER MULTIPLE BIRTH, SOME LIVE BORN |
| V27.9x | UNSPECIFIED |

ICD-10-CA Equivalent Codes

| ICD-10-CA Code | Description |
|-----------------------|--------------------------------------|
| Z37.3x | TWINS, ONE LIVE BORN AND ONE |
| Z37.6x | OTHER MULTIPLE BIRTH, SOME LIVE BORN |
| Z37.9x | UNSPECIFIED |

Major Congenital Malformations

Major congenital malformations were defined using the European Surveillance of Congenital Anomalies (EUROCAT), International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), and Public Health Agency of Canada classifications, with some modifications (Pasternak et al, 2013).

1. We extracted all physician visits during the follow-up with diagnosis codes of congenital malformations, based on the list of codes in the table at the end of this section, column ‘A’.
2. We extract all hospitalizations with any diagnosis code of a congenital malformation (based on codes in the table below) and admission date. For records with ICD-9, we checked each diagnosis variable individually, and selected the record if the code was included in Column ‘B’ but not in Column ‘C’. For example, if the diagnosis code was 743.x, but not 743.6 or 743.8, then we included the malformation. If the code was 743.6 we excluded the malformation. We repeated this process using Columns ‘D’ and ‘E’.

Table: ICD Codes Used to Identify Malformations

| Category | Physician Services | Hospital Services | | | |
|-------------------------|--------------------|-------------------|---|-------------|--|
| | ICD-9: 3 digits | ICD-9: 4 digits | *Exclusion for minor anomalies | ICD-10 | *Exclusion for minor anomalies |
| Column | A | B | C | D | E |
| Nervous system | 740-742 | 740.0–742.9 | | Q00.0–Q07.9 | |
| Eye, ear, face and neck | 743, 744 | 743.0-744.9 | 743.6, 743.8, 744.1-744.9 | Q10.0-Q18.9 | Q10.0-10.6, Q13.0, Q13.2, Q13.5, Q15.8, Q17.0-Q17.5, Q17.8, Q17.9, Q18.0-Q18.9 |
| Circulatory system | 745-747 | 745.0-747.9 | 747.0, 747.5 | Q20.0-Q28.9 | Q25.0, Q27.0 |
| Respiratory | 748 | 748.0-748.9 | 748.2, 748.3 | Q30.0-Q34.9 | Q30.2, Q30.8, Q31-Q32, Q33.1 |
| Orofacial clefts | 749 | 749.0-749.2 | | Q35.0-Q37.9 | Q35.7 |
| Digestive system | 750, 751 | 750.0-751.9 | 750.0, 750.1, 750.2, 750.5, 750.6, 751.0, 751.5 | Q38.0-Q45.9 | Q38.1-Q38.6, Q40.0, Q40.1, Q43.0, Q43.4-Q43.9 |

| Category | Physician Services | Hospital Services | | | |
|------------------------|--------------------|--------------------|--|---------------------------|---|
| | ICD-9: 3 digits | ICD-9: 4 digits | *Exclusion for minor anomalies | ICD-10 | *Exclusion for minor anomalies |
| Column | A | B | C | D | E |
| Genital organs | 752 | 752.0-752.9 | 752.4, 752.5, 752.8 | Q50.0-Q56.9 | Q52.2, Q52.3, Q52.4, Q52.5, Q52.6, Q52.7, Q52.8, Q53, Q54.4, Q55.1, Q55.2, Q55.6, Q55.8, Q55.9 |
| Urinary system | 753 | 753.0-753.9 | 753.6 | Q60.0-Q64.9 | Q61.0, Q62.7, Q63.3, Q64.2-Q64.3 |
| Musculoskeletal system | 754-756 | 754.0-756.9 | 754.0, 754.1, 754.7, 754.8, 756.0, 756.2 | Q65.0-Q79.9 | Q65.3-Q65.6, Q66.2, Q66.3, Q66.5-Q66.9, Q67.0-Q67.4, Q67.6-Q67.8, Q68.0, Q68.1, Q68.3-Q68.8, Q70.3, Q74.1, Q75.0, Q75.2, Q75.3, Q75.8, Q76.0, Q76.5, Q79.5, Q79.8 |
| Integument | 757** | 757.0-757.9 | 757.2, 757.3, 757.4, 757.5, 757.6, 757.8 | Q80.0-Q84.9 | Q81, Q82.1-Q82.8, Q83.2, Q83.3, Q83.8, Q84.1, Q84.2, Q84.3, Q84.4, Q84.5, Q84.6, Q84.8 |
| Chromosomal | 758 | 758.0-758.8 | 758.4 | Q90.0-Q99.2 | Q95.0, Q95.1 |
| Other | 759 | 758.9, 759.0-759.9 | 759.9 | Q85.0-Q89.9, Q99.8, Q99.9 | Q89.9 |

Congenital malformations were excluded if they were on our list of excluded malformations defined in the following two tables.

Table: Specific Congenital Malformations linked to Medication Use

| Category | Hospital Services | | | |
|----------------------------|-------------------|--------------------------------|--------|--------------------------------|
| | ICD-9 | *Exclusion for minor anomalies | ICD-10 | *Exclusion for minor anomalies |
| Isolated cleft palate | 749.0 | | Q35.x | Q35.7 |
| Ventricular septal defects | 745.4 | | Q21.0 | |
| Tetralogy of Fallot | 745.2 | | Q21.3 | |
| Hypoplastic left heart | 747.7 | | Q23.4 | |

| Category | Hospital Services | | | |
|----------------------|-------------------|--------------------------------|-------------|--------------------------------|
| | ICD-9 | *Exclusion for minor anomalies | ICD-10 | *Exclusion for minor anomalies |
| Cardiac overall | 745.x-747.2x | 747.0 | Q20.x-Q26.x | Q25.0 |
| Diaphragmatic hernia | 756.6 | | Q79.0 | |

Table Other Excluded Anomalies

| | ICD-9 | ICD-10 |
|-----------------------------|--|---|
| Anomalies with known causes | 760.7 | Q86 |
| Chromosomal anomalies | 758 | Q90-99 |
| Genetic syndromes | 756.4, 756.3, 756.8, 759.5, 759.6, 759.8 | Q75.1, Q75.4, Q77.1, Q77.2, Q79.6, Q85, Q87 |
| Congenital virus infections | 771.0, 771.1, 771.2, 771.2 | P35.0, P35.1, P35.2, P371 |

ADDITIONAL NOTES ON CPRD:

Regarding the CPRD, we included pregnancies identified in the CPRD pregnancy register, which uses a validated algorithm (<https://pubmed.ncbi.nlm.nih.gov/31197928/>) to identify pregnancies from the general practitioner records. This register includes a unique identifier for the mother and pregnancy, the date of delivery, the estimated gestational age, and the pregnancy outcome. We used the ‘Gold’ version of the CPRD, as a pregnancy register is not yet available for CPRD AURUM. CPRD primary care records (including the pregnancy register) were linked to hospitalization data (acute patient care and maternity) from Hospital Episode Statistics (HES) and Office for National Statistics (ONS) vital statistics data, with inclusion restricted to linkable patients. Pregnancy outcomes were defined using the outcome variable in the CPRD pregnancy register. Congenital malformations were defined using diagnoses recorded in maternal and offspring CPRD and HES records, with the offspring identified using the Mother-Baby linkage. Comorbidities were defined using Read codes in CPRD primary care data and ICD-10 codes from HES, and prescription drug information was assessed using product codes and BNF codes recorded in general practitioner prescription records. ONS vital statistics data were used to supplement CPRD and HES data to define censoring.

For the CPRD analysis of congenital malformations, we used the CPRD Mother-Baby link to identify the offspring records in the CPRD. The Mother-Baby Link was created using a cartesian join of mothers to babies using the general practitioner practice identification number and the practice-specific family number, with inclusion restricted to records whose delivery date and estimated birth date are within 60 days.

EAPPENDIX 4: EXPOSURE ASCERTAINMENT METHODOLOGY

For the main analysis, exposure was assessed as follows:

Once a woman was exposed to ondansetron or a comparator antiemetic, she was considered exposed until the end of the follow-up (end of pregnancy).

Once a woman started contributing person-time to the comparator antiemetic category, she could only subsequently switch her exposure status to ondansetron. If a woman tried another antiemetic after ondansetron, her exposure status remained defined as ondansetron-exposed.

A woman could not contribute person-time to two different exposure categories at the same time.

In rare instances where a woman started NVP pharmacotherapy simultaneously with ondansetron and a comparator antiemetic, she was assigned to the ondansetron-exposed category.

The table below provides information on the eligible windows during pregnancy during which exposure was assessed. Note: the term COHORTENTRYDT denotes the first day of pregnancy. This variable name was not used in the manuscript text.

Table: Exposure Assessment Windows

| Event Type | Exposure Assessment Window (Drug dispensed during window) |
|---|--|
| Primary Outcome | |
| Fetal Death (stillbirth or spontaneous abortion) | In order to enter cohort, exposed to a study and or comparator drug \geq COHORTENTRYDT, until, but not including, the outcome date (Sensitivity analysis of exposure between 4 and 10 weeks: In order to enter cohort, exposed to a study and or comparator drug \geq COHORTENTRYDT + 27 days, until the earliest of COHORTENTRYDT + 69 days or up to and including the day <u>before</u> the outcome; but NOT exposed to a study and or comparator drug \geq COHORTENTRYDT and $<$ COHORTENTRYDT + 27) |
| Secondary Outcomes | |
| Stillbirth | In order to enter cohort, exposed to a study and or comparator drug \geq COHORTENTRYDT, until outcome date, until, but not including, the outcome date (Sensitivity analysis: In order to enter cohort, exposed to a study and or comparator drug \geq COHORTENTRYDT + 27 days, until the earliest of COHORTENTRYDT + 69 days, or up to and including the day <u>before</u> the outcome; but NOT exposed to a study and or comparator drug \geq COHORTENTRYDT and $<$ COHORTENTRYDT + 27) |
| Spontaneous Abortion | In order to enter cohort, exposed to a study and or comparator drug \geq COHORTENTRYDT, until the earliest of COHORTENTRYDT + 140 days, or up to and including the day <u>before</u> the outcome |

| | |
|-------------------------------|--|
| | (Sensitivity analysis: In order to enter cohort, exposed to a study and or comparator drug \geq COHORTENTRYDT + 27 days, until the earliest of COHORTENTRYDT + 69 days, or up to and including the day <u>before</u> the outcome; but NOT exposed to a study and or comparator drug \geq COHORTENTRYDT and $<$ COHORTENTRYDT + 27) |
| Major Congenital Malformation | In order to enter cohort, exposed to a study and or comparator drug COHORTENTRYDT to COHORTENTRYDT + 83 days, inclusive. (Sensitivity analysis: In order to enter cohort, exposed to a study and or comparator drug \geq COHORTENTRYDT + 27 days, until COHORTENTRYDT + 69 days, inclusive) |