Available medications used as potential therapeutics for COVID-19: What are the known safety profiles in pregnancy

Anick Bérrard1,2,3*, Odile Sheehy1, Jin-Ping Zhao1, Evelyne Vinet4, Caroline Quach1,5, Behrouz Kassai3, Sasha Bernatsky4

1 Research Center, CHU Sainte-Justine, Montreal, Quebec, Canada, 2 Faculty of Pharmacy, University of Montreal, Montreal, Quebec, Canada, 3 Faculty of Medicine, Université Claude Bernard, Lyon, France, 4 Faculty of Medicine, McGill University, Montreal, Quebec, Canada, 5 Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada

*anick.berard@umontreal.ca

Abstract

Background
Medications already available to treat other conditions are presently being studied in clinical trials as potential treatments for COVID-19. Given that pregnant women are excluded from these trials, we aimed to investigate their safety when used during pregnancy within a unique population source.

Methods
Using the population-based Quebec Pregnancy Cohort, we identified women who delivered a singleton liveborn (1998–2015). Taking potential confounders into account including indications for use, the risk of prematurity, low birth weight (LBW), small for gestational age (SGA), and major congenital malformation (MCM) associated with COVID-19 repurposed drug use during pregnancy were quantified using generalized estimation equations.

Results
Of the 231,075 eligible pregnancies, 107 were exposed to dexamethasone (0.05%), 31 to interferons (0.01%), 1,398 to heparins (0.60%), 24 to angiotensin-receptor blockers (ARB) (0.01%), 182 to chloroquine (0.08%), 103 to hydroxychloroquine (0.05%), 6,206 to azithromycin (2.70%), 230 to oseltamivir (0.10%), and 114 to HIV medications (0.05%). Adjusting for potential confounders, we observed an increased risk of prematurity related to dexamethasone (aOR 1.92, 95%CI 1.11–3.33; 15 exposed cases), anti-thrombotics (aOR 1.58, 95%CI 1.31–1.91; 177 exposed cases), and HIV medications (aOR 2.04, 95%CI 1.01–4.11; 20 exposed cases) use. An increased risk for LBW associated with anti-thrombotics (aOR 1.72, 95%CI 1.41–2.11; 152 exposed cases), and HIV medications (aOR 2.48, 95%CI 1.25–4.90; 21 exposed cases) use were also found. Gestational exposure to anti-thrombotics (aOR 1.20, 95%CI 1.00–1.44; 176 exposed cases), and HIV medications (aOR 2.61, 95%CI 1.51–4.51; 30 exposed cases) were associated with SGA. First-trimester
dexamethasone (aOR 1.66, 95%CI 1.02–2.69; 20 exposed cases) and azithromycin (aOR 1.10, 95%CI 1.02–1.19; 747 exposed cases) exposures were associated with MCM.

Conclusions

Many available medications considered as treatments for COVID-19 are associated with adverse pregnancy outcomes. Caution is warranted when considering these medications during the gestational period.

Introduction

Given the changes to the cardiopulmonary and immune systems during pregnancy, pregnant women are at increased risk for severe COVID-19 [1–3]. In June 2020, the US Centers for Disease Control and Prevention reported that pregnant women with COVID-19 were more likely to be hospitalized and at increased risk for intensive care unit (ICU) admission and receipt of mechanical ventilation compared with non-pregnant women of reproductive age [4]. The World Association of Perinatal Medicine Working Group on COVID-19, with data from Europe, the US, South America, Asia and Australia reported a 0.8% rate of mortality and a 11.1% rate of ICU admissions among infected pregnant women; vertical transmission was negligible [5]. Although vaccination is underway in many countries, pregnant women are often advised against it due to missing data on safety and efficacy during pregnancy. Medications already available to treat other conditions are presently being studied in clinical trials as potential treatments for COVID-19. However, given that pregnant women are excluded from these trials, it is important to assess the current safety profile of these drugs in pregnancy. According to the WHO COVID-19, BMJ COVID-19 Hub, JAMA Network COVID-19, The Lancet COVID-19 Resource Center, New England Journal of Medicine COVID-19, and CMAJ COVID-19 registered trials, these medications include dexamethasone, interferon, heparins, angiotensin-receptor blockers (ARB), chloroquine, hydroxychloroquine, azithromycin, oseltamivir, and HIV medications [6].

At present, results from the COVID-19 RECOVERY trial showed that dexamethasone reduced the mortality rates in severe COVID-19 non-pregnant patients requiring oxygen therapy or on ventilator support [7], as the immunosuppressant dexamethasone may be countering the effect of the cytokine in immune dysregulated severe COVID-19 patients [8–11]. Cortisol is critical for embryogenesis, and endogenous fetal glucocorticoid levels remain significantly lower than maternal levels throughout gestation [12,13]; exogenous corticosteroids across the placenta could have adverse developmental effects [14]. Early pregnancy corticosteroid use has been associated with increased risk of orofacial cleft in some [15–20], but not in recent studies [21,22]. Furthermore, studies have reported an increased risk of preterm birth or shorter gestational length following oral corticosteroid use during pregnancy among women with autoimmune disease [23,24].

Likewise, in a phase 2 randomized trial, the immunomodulator interferon beta-1b combined with protease inhibitors (lopinavir–ritonavir) and a nucleoside analogue (ribavirin) was superior to lopinavir–ritonavir alone in reducing the duration of the viral shedding, symptom alleviation, and hospital stay in patients with COVID-19 [25].

About 20%–55% of severe COVID-19 patients have laboratory evidence of coagulopathy [26] and the use of anticoagulant therapy with heparin showed to decrease mortality [27]. Heparin in pregnancy is widely accepted and experienced in women with a high risk of
thromboembolism and other conditions; in small sample size studies, heparin use during pregnancy has not shown to be putting the fetus at risk [28].

Angiotensin-converting receptors (ACE2) are required for SARS-CoV2 to enter human cells [29,30]. ACE inhibitors and ARBs are often taken as first-line treatment for hypertension [31], which can result in increased ACE2 expression [32], and increased viral load [33]. Thus, the use of ACE inhibitors or ARBs may aggravate the severity or worsen the outcome of COVID-19 [34,35]. Although ACE inhibitors are contraindicated during pregnancy, ARBs continue to be used inadvertently [36]. At present, ACE inhibitors and ARBs have been shown to be associated with major malformations [36], intrauterine growth retardation, renal dysplasia, anuria, renal failure and death [37–41].

Chloroquine and hydroxychloroquine are currently used to treat and prevent malaria, as well as treat rheumatic diseases. Although many trials have been done on their effectiveness for the treatment of COVID-19, results are conflicting with anecdotal case reports [42–44]. Chloroquine and hydroxychloroquine cross the placenta with a half-life of around 50 days, which could lead to long-term effect during gestation [45]. However, when used for malaria, lupus, or rheumatoid arthritis, hydroxychloroquine was not shown to increase adverse pregnancy outcomes [46]. Other drugs such as azithromycin and oseltamivir, and HIV protease inhibitors indinavir, saquinavir and raltegravir may inhibit the replication of SARS-CoV-2 and have been used in COVID-19 clinical trials [47–50]. Antiretroviral therapy, specifically protease inhibitors, use during pregnancy has been associated with increased risk of preterm birth in some studies [51–59], as antiretroviral therapy produces immunologic changes [60], and interfering with maintenance of pregnancy [61]. A potential safety signal for an increased rate of neural tube defects in association with dolutegravir use in pregnancy has been identified in the surveillance study in Botswana [62], but not in other studies [63–65].

Although immunomodulator dexamethasone and interferon, anticoagulant heparins, angiotensin-receptor blockers (ARB), chloroquine, hydroxychloroquine as well as azithromycin, oseltamivir, and HIV medications are being considered in clinical trials for COVID-19 treatments, their safety in pregnancy need to be determined.

As of now, all these medications have been studied independently in different pregnant populations and not for the treatment of COVID-19 during pregnancy, which makes safety comparisons difficult. Also, these studies would likely not capture pregnant women concomitantly taking more than one COVID-19 potential available treatments, which is highly likely to occur in clinical practice. Finally, different classifications of medication exposure and disease outcomes between studies would lead to imperfect comparisons with regards to safety.

We therefore aimed to quantify the effect of COVID-19 potential available therapeutics, based on the WHO list of registered medication trials, during pregnancy on the risk of pretermity, low birth weight (LBW), small for gestational age (SGA), and major congenital malformations (MCM) using real-world data.

Methods

Study cohort

We analyzed data from the Quebec Pregnancy Cohort (QPC), which is a population-based cohort with prospective data collection on all pregnancies covered by the province of Quebec’s universal prescription drug insurance, from 01/01/1998 to 31/12/2015 [66]. Individual-level information for all pregnant women and children are obtained from province-wide databases and linked using unique personal identifiers (S1 Fig). We defined the first day of the last menstrual period (LMP) using data on gestational age, which has been validated against ultrasound
measures from each patients’ charts within the QPC [67]. Prospective follow-up is available from 1 year before LMP, during pregnancy, and until 31/12/2015 (S2 Fig).

The QPC data sources include the medical claims database (‘Régie de l’assurance maladie du Québec’ (RAMQ): diagnoses, medical procedures, socio-economic status), Quebec’s outpatient prescription drug insurance database (drug name, start date, dosage, duration), hospitalization archives database (MedEcho: in-hospital diagnoses and procedures, gestational age), and the Quebec birth certificates database (‘Institut de la statistique du Québec’ (ISQ): patient socio-demographics, gestational age, birth weight). Birth weight in ISQ, and MCM and other diagnoses in the RAMQ and MedEcho databases have been found to be valid when compared to patient charts [67,68].

Pregnant women in the QPC were eligible for this study if they were i) more than 18 years old; ii) continuously covered by the Quebec prescription drug insurance for ≥12 months before pregnancy and during pregnancy; and iii) had given birth to a liveborn singleton. This was done because twin pregnancies are at increased risk of adverse pregnancy outcomes regardless of gestational medication exposures. We also excluded pregnancies exposed to known teratogens as described by Kulaga et al. [69] (S1 Table), and those resulting in minor malformations alone or chromosomal abnormalities in the newborns for analyses on MCM. Minor malformations are selectively identified and do not reflect the true prevalence; chromosomal abnormalities are not related to medication use.

**Ethics statement.** The study was approved by the Sainte-Justine’s Hospital Ethics Committee. The Quebec “Commission d’accès à l’information” authorized database linkages. All data were fully anonymized before we accessed them, and the Ethics Committee of CHU Sainte-Justine as well as the ‘Commission d’accès à l’information’ waived the requirement for informed consent.

**Study medication exposures**

Study medications included outpatient filled prescriptions of immunomodulator dexamethasone, interferon for multiple sclerosis (beta-1a, beta-1b, and alfa-2b), antithrombotic heparin and heparin derivatives (enoxaparin, dalteparin, and tinzaparin), ARB (losartan and telmisartan), chloroquine, hydroxychloroquine, azithromycin, oseltamivir, and HIV medications (indinavir, lopinavir/ritonavir, saquinavir and raltegravir). We identified study medication prescription fillings from the Quebec prescription drug insurance database (prescribed over-the-counter medications were also included), using timing of exposure determined by the dispensed date and duration of treatment. Pregnancies were dichotomously defined as exposed within each of the study medication groupings if women had filled at least one study medication during pregnancy or if they had filled a prescription with a duration that overlapped the beginning of pregnancy (yes/no). Pregnant women could use more than one study medication during the gestational period, and thus were considered in each corresponding study medication grouping when that was the case. The exposure time window for analyses on prematurity, LBW and SGA was any time during pregnancy; only first trimester exposure (organogenesis) was considered for analyses on MCM.

Data on prescription fillings have been validated and compared to maternal reports in the QPC; the positive predictive value (PPV) of prescription drug data was ≥87% (95%CI: 70%-100%) and the negative predictive value (NPV) was ≥92% (95%CI: 86%-98%) [70].

**Outcomes**

Cases of prematurity were identified from the RAMQ and MedEcho databases and defined as deliveries before the 37th week of gestation.
Cases of LBW were identified from the ISQ database as newborns with birthweight less than 2,500g.

Cases of SGA were identified from the MedEcho database (gestational age) and the ISQ database (birth weight and sex) and were defined as birthweights below the 10th percentile for newborns of the same gestational age and the same sex, according to population-based Canadian references [71]. Birth weight in ISQ and gestational age in MedEcho have been found to be valid when compared to patient charts [67,68].

Cases of MCM diagnosed in the first 12 months of life were identified from the RAMQ and MedEcho databases and defined according to ICD-9 and ICD-10 codes (S2 Table), which have been validated against patient charts with high PPV (78.1%) and NPV (94.2%) [68]. All organ systems were considered and high PPV (over 80%) have also been reported for specific MCMs [68]. Twelve months after birth was needed to allow for late detection, and validation of early diagnoses.

**Statistical analyses**

Within the identified study cohort, we conducted 4 case-control analyses to quantify the effect of the study medication exposures during pregnancy on the occurrence of prematurity, LBW, SGA, and MCM. Although case-control analyses were performed within the study cohort, we have included all controls (no control sampling has been done), and therefore, odds ratios (OR) give the same estimate measure as relative risks.

Potential confounders considered for all analyses were: 1) sociodemographic variables on LMP including maternal age, welfare recipients (yes/no), area of residence (urban/rural); 2) maternal chronic comorbidities (in the 12 months before pregnancy and during pregnancy identified by a diagnosis code or a medication-specific filling) including diabetes, asthma, thyroid disorders (see S3 Table for diagnostic and medication codes used); 3) Tobacco, alcohol, and illicit drug use (See S3 Table); 4) Health care utilization including hospitalizations or emergency department visits during pregnancy (yes/no), number of general practitioner visits and specialist visits (12 months pre-pregnancy); 5) Pregnancy related variables including folic acid use (prescribed high dose (>5 mg/d) and prescribed over-the-counter (OTC) dosage only) in the 6-months prior to LMP and during pregnancy (S3 Table), and previous pregnancy (spontaneous or planned abortion, delivery) in the year prior to LMP (yes/no). We also considered whether pregnant women were followed by an obstetrician (yes/no), and if other medications were used during pregnancy (besides the study medications and medication used to identify comorbidities).

Finally, to control for potential confounding by indication, we adjusted for the presence of the following indications during pregnancy (a pregnant women could have multiple comorbidities): malaria (ICD-9 code 084 and ICD-10 codes B50-B54), lupus (ICD-9 codes 695.4, 710.0 and ICD-10 codes L93, M32), arthritis (ICD-9 codes 274, 696.0, 710.3, 710.4, 714 and ICD-10 codes L40.5, M05, M06, M08, M10, M33.10, M33.20), respiratory tract infections and disorders (ICD-9 codes 011.90, 135, 381, 382, 461, 466, 491.21, 503, 518.3 and ICD-10 codes A15.0, D86, H65-H67, J01-J03, J17, J18, J63.2, J44.1, J82), sexually transmitted diseases and urinary tract infection (ICD-9 codes 077, 099.0, 310, 597–599, 614, 616.0 and ICD-10 codes A31, A54-A57, N34, N37, N70-N77), thrombosis and antiphospholipid syndrome (ICD-9 codes 289.81, 415.19, 444, 453 and ICD-10 codes D68.61, I23, I26, I74, I82), skin disorders (ICD-9 codes 202.1, 694.0, 694.4, 695.1, 695.9 codes and ICD-10 codes C84.0, L10, L13.0, L51.1, L53.9), endocrine disorders (ICD-9 codes 245.0, 255.2, 255.4, 275.4 and ICD-10 codes E06.9, E25.0, E27, E83.52), gastro-intestinal disorders (ICD-9 code 555.9 and ICD-10 codes K50, K51), other hematologic disorders (ICD-9 codes 283, 284, 287.31, 287.4 and ICD-10 codes...
codes D59, D60, D61, D69.3, D69.59), human immunodeficiency virus (HIV) (ICD-9 codes 042, 043, 044 and ICD-10 code B20), hepatitis B or C (ICD-9 codes 070.2, 070.3, 070.7 and ICD-10 code B18.2), hypertension (ICD-9 code 401 and ICD-10 code I10), influenza (ICD-9 code 487 and ICD-10 codes J09–J11).

All study medication groupings were always included in analyses, which ensured that estimates were adjusted for concomitant study medication use.

The unit of analysis was a pregnancy. Means and proportions for continuous and dichotomous variables were calculated, respectively. Crude and adjusted odds ratios (aOR) with 95% confidence intervals (95%CI) were calculated for each outcome separately. Multivariable generalized estimating equations were used to estimate the association between the study medications and the risk of prematurity, LBW, SGA, and MCM, independently, accounting for clustering by family (mother). All above mentioned potential confounders and covariables were included in all analyses. All statistical analyses were performed using SAS (SAS Institute Inc., Version 9.2, Cary, NC, USA).

Results

Of the 248,787 pregnancies with a delivery within the QPC, 231,075 met inclusion criteria and were considered for analyses; 8,213 pregnancies were exposed to at least one COVID-19 repurposed drug (Fig 1). We identified 182 pregnancies exposed to chloroquine (0.08%), 103 to hydroxychloroquine (0.05%), 107 to dexamethasone (0.05%), 1,398 to anti-thrombotics (enoxaparin, dalteparin, and tinzaparin, 0.60%), 31 to multiple sclerosis study medications (interferon beta-1a, beta-1b, and alfa-2b, 0.01%), 6,206 to azithromycin (2.70%), 114 to HIV medications (indinavir, lopinavir/ritonavir, raltegravir and saquinavir, 0.05%), 230 to osel tamivir (0.10%), and 24 to the study ARB (losartan and telmisartan, 0.01%) (Fig 1, Table 1).

Study medication users were slightly older; welfare recipients (33.3% vs. 22.5% in non-users); more likely to use high dose (>5 mg/d) folic acid; more likely to have hypertension, diabetes or asthma; and had a higher prevalence of health services utilization including other medication use (Table 1).

Within the study population, 6.5% (15,032) pregnancies resulted in a premature delivery. Adjusting for potential confounders, dexamethasone (aOR 1.92, 95%CI 1.11–3.33; 15 exposed cases), anti-thrombotics (aOR 1.58, 95%CI 1.31–1.91; 177 exposed cases), and HIV medications (aOR 2.04, 95%CI 1.01–4.11; 20 exposed cases) use during pregnancy were statistically significantly associated with an increased risk of prematurity (Table 2A).

LBW has been identified in 5.0% (11,606) of newborns. Adjusting for potential confounders including indication for use, anti-thrombotics (aOR 1.72, 95%CI 1.41–2.11; 152 exposed cases), and HIV medications (aOR 2.48, 95%CI 1.25–4.90; 21 exposed cases) were statistically significantly associated with an increased risk of LBW (Table 2B).

Nine percent (9.6%, 22,280) of pregnancies resulted in an SGA newborns. Adjusting for potential confounders including indication for use, anti-thrombotics (aOR 1.20, 95%CI 1.00–1.44; 176 exposed cases), and HIV medication use (aOR 2.61, 95%CI 1.51–4.51; 30 exposed cases) were statistically significantly associated with an increased risk of SGA (Table 2C).

Overall MCM were identified in 10.4% (23,991) of pregnancies. Adjusting for potential confounders, dexamethasone (aOR 1.66, 95%CI 1.02–2.69; 20 exposed cases) and azithromycin (aOR 1.10, 95%CI 1.02–1.19; 747 exposed cases) use during pregnancy were statistically significantly associated with an increased risk of MCM (Table 2D).

Table 3 presents organ specific defects identified with the use of the study medications. Musculoskeletal defects and circulatory malformations including heart defects were the most...
Fig 1. Cohort selection within the Quebec Pregnancy Cohort.

https://doi.org/10.1371/journal.pone.0251746.g001

1Heparin, dalteparin, enoxaparin, and tinzaparin.
2Beta-1A, beta-1B, and alfa-2B interferons.
3Indinavir, lopinavir/ritonavir, raltegravir, and saquinavir.
4Angiotensin-receptor blockers (ARB): Losartan, losartan / HCTZ, telmisartan, telmisartan / HCTZ.
Table 1. Study medication exposures during pregnancy, n = 8,213

| Characteristic | Non exposed to any of the study drugs | Chloroquine | Hydroxychloroquine | Dexamethasone | Anti-thrombotics |
|----------------|--------------------------------------|-------------|--------------------|---------------|-----------------|
| Mean maternal age (years) | 28.2 (5.6) | 28.8 (5.6) | 26.8 (7.0) | 29.0 (5.6) | 28.1 (5.2) |
| Mean gestational age (weeks) | 35.7 (1.7) | 35.2 (1.7) | 35.5 (2.1) | 35.3 (2.1) | 35.2 (1.7) |

At the first day of gestation (1DG):

- **Mean maternal age (years):**
  - Chloroquine: 28.2 (5.6)
  - Hydroxychloroquine: 28.8 (5.6)
  - Dexamethasone: 29.0 (5.6)
  - Anti-thrombotics: 28.1 (5.2)

- **Welfare recipients—n (%):**
  - Chloroquine: 50,089 (22.5)
  - Hydroxychloroquine: 13 (7.1)
  - Dexamethasone: 33 (32.0)
  - Anti-thrombotics: 34 (31.8)

- **Urban dweller—n (%):**
  - Chloroquine: 183,266 (82.2)
  - Hydroxychloroquine: 146 (80.2)
  - Dexamethasone: 87 (84.5)
  - Anti-thrombotics: 85 (85.9)

Specific indications for the study medication exposures—n (%):

- **Malaria:**
  - Chloroquine: 90 (0.4)
  - Hydroxychloroquine: 2 (1.1)
  - Dexamethasone: 0 (0.0)
  - Anti-thrombotics: 0 (0.0)

- **Lupus:**
  - Chloroquine: 118 (0.5)
  - Hydroxychloroquine: 1 (0.5)
  - Dexamethasone: 45 (43.7)
  - Anti-thrombotics: 2 (1.8)

- **Arthritis:**
  - Chloroquine: 878 (41.2)
  - Hydroxychloroquine: 6 (6.8)
  - Dexamethasone: 35 (33.8)
  - Anti-thrombotics: 10 (9.3)

Available medications used as therapeutics for COVID-19: What are the known safety profiles in pregnancy

PLOS ONE | https://doi.org/10.1371/journal.pone.0251746 May 19, 2021 8 / 24
### Study medications exposure during pregnancy, n = 8,213

| Characteristics | Non exposed to any of the study drugs | Chloroquine | Hydroxychloroquine | Dexamethasone | Anti-thrombotics | Multiple sclerosis medications | Azithromycin | HIV medications | Oseltamivir | ARB |
|-----------------|--------------------------------------|-------------|--------------------|---------------|-----------------|---------------------------|--------------|----------------|------------|-----|
| Mean duration (weeks) of pregnancy ± SD | 38.9 ± 1.8 | 39.0 ± 2.0 | 38.2 ± 1.8 | 38.1 ± 2.7 | 38.0 ± 2.1 | 38.8 ± 1.2 | 38.8 ± 1.8 | 38.0 ± 2.1 | 38.8 ± 1.5 | 38.5 ± 2.0 |
| Mean birthweight (g) ± SD | 3352.8 ± 542.3 | 3387.1 ± 561.4 | 3102.2 ± 568.6 | 3188.5 ± 653.6 | 3158.8 ± 612.5 | 3232.9 ± 412.2 | 3306.2 ± 540.0 | 2985.0 ± 592.7 | 3316.3 ± 509.7 | 3235.3 ± 591.5 |
| Prematurity—n (%) | 14,310 (6.4) | 12 (6.6) | 13 (12.6) | 15 (14.0) | 177 (12.7) | 0 (0.0) | 472 (7.6) | 20 (17.5) | 11 (4.8) | 2 (8.3) |
| LBW—n (%) | 10,991 (4.9) | 9 (5.0) | 13 (12.6) | 10 (9.4) | 152 (10.9) | 0 (0.0) | 390 (6.3) | 21 (18.4) | 17 (7.4) | 3 (12.5) |
| SGA—n (%) | 21,351 (9.6) | 12 (6.6) | 16 (15.5) | 10 (9.4) | 176 (12.6) | 3 (9.7) | 656 (10.6) | 30 (26.3) | 26 (11.3) | 2 (8.3) |
| Major congenital malformation—n (%) | 22,952 (10.3) | 14 (7.7) | 16 (15.5) | 20 (18.7) | 191 (13.7) | 2 (6.5) | 747 (12.0) | 16 (14.0) | 29 (12.6) | 4 (16.7) |
| Maternal comorbidities in the year prior to or during pregnancy | Diabetes—n (%) | 4,883 (2.2) | 4 (2.2) | 8 (7.8) | 20 (18.7) | 107 (7.7) | 1 (3.2) | 205 (3.3) | 7 (6.1) | 13 (5.7) | 1 (4.2) |
| Asthma—n (%) | 26,099 (11.7) | 26 (14.3) | 19 (18.5) | 21 (19.6) | 241 (17.2) | 8 (25.8) | 1,495 (24.1) | 21 (18.4) | 43 (18.7) | 6 (25.0) |
| Thyroid disorders—n (%) | 9,810 (4.4) | 9 (5.0) | 16 (15.5) | 17 (15.9) | 96 (6.9) | 3 (9.7) | 314 (5.1) | 3 (2.6) | 747 (12.0) | 16 (14.0) | 29 (12.6) | 4 (16.7) |
| Tobacco dependence—n (%) | 6,872 (3.1) | 2 (1.1) | 5 (4.9) | 5 (4.7) | 71 (5.1) | 2 (6.5) | 367 (5.9) | 2 (1.8) | 10 (4.4) | 0 (0.0) |
| Alcohol dependence—n (%) | 857 (0.4) | 1 (0.6) | 1 (1.0) | 0 (0.0) | 7 (0.5) | 0 (0.0) | 46 (0.7) | 0 (0.0) | 2 (0.9) | 0 (0.0) |
| Other drug dependence—n (%) | 2,185 (1.0) | 1 (0.6) | 4 (3.9) | 1 (0.9) | 21 (1.5) | 1 (3.2) | 140 (2.3) | 9 (7.9) | 3 (1.3) | 0 (0.0) |

#### General practitioner visits (in the year prior to pregnancy):
- **Mean number of visits ± SD**:
  - 4.4 ± 5.7
  - 4.0 ± 4.6
  - 6.4 ± 7.7
  - 5.6 ± 7.6
  - 5.8 ± 8.2
  - 6.6 ± 6.8
  - 5.8 ± 7.2
  - 5.1 ± 7.6
  - 6.3 ± 8.5
  - 6.3 ± 5.5

- **Number of visits—n (%):**
  - 0: 47,382 (21.3)
  - 1: 32,809 (14.7)
  - 2–4: 69,383 (31.1)
  - ≥ 5: 73,288 (32.9)

#### Specialist visits (in the year prior to pregnancy):
- **Mean number of visits ± SD**: 3.4 ± 6.2, 2.7 ± 3.7, 11.4 ± 14.1, 7.7 ± 14.4, 8.3 ± 11.9, 6.7 ± 6.5, 4.2 ± 8.6, 6.4 ± 7.9, 3.7 ± 5.8, 2.6 ± 2.6

- **Number of visits—n (%):**
  - 0: 88,122 (39.5)
  - 1–2: 55,633 (25.0)
  - ≥ 3: 79,107 (35.5)
Table 1. (Continued)

| Characteristics | Non exposed to any of the study drugs | Chloroquine | Hydroxychloroquine | Dexamethasone | Anti-thrombotics<sup>1</sup> | Multiple sclerosis medications<sup>2</sup> | Azithromycin | HIV medications<sup>3</sup> | Oseltamivir | ARB<sup>4</sup> |
|-----------------|---------------------------------------|-------------|--------------------|---------------|-----------------|-----------------|----------------|-----------------|-------------|------------|
| Other prescribed medications (during pregnancy): | | | | | | | | | | |
| Mean ± SD | 1.7 ± 2.1 | 2.5 ± 2.5 | 5.5 ± 3.7 | 5.5 ± 3.8 | 4.4 ± 3.8 | 3.9 ± 3.0 | 3.4 ± 3.3 | 5.8 ± 3.4 | 3.5 ± 3.5 | 5.4 ± 3.4 |
| Number of medications—n (%) | 0 | 83,159 (37.3) | 28 (15.4) | 8 (7.8) | 3 (2.8) | 83 (5.9) | 1 (0.0) | 37 (16.1) | 1 (4.2) |
| 1–2 | 84,932 (38.1) | 81 (44.5) | 15 (14.6) | 20 (18.7) | 415 (29.7) | 10 (32.3) | 2,196 (35.4) | 13 (11.4) | 76 (33.0) | 5 (20.8) |
| ≥ 3 | 54,771 (24.6) | 73 (40.1) | 80 (77.7) | 84 (78.5) | 900 (64.4) | 20 (64.5) | 3,180 (51.2) | 101 (88.6) | 117 (50.9) | 18 (75.0) |
| Hospitalization/ Emergency Department visit during pregnancy | 74,739 (33.5) | 53 (29.1) | 49 (47.6) | 40 (37.4) | 690 (49.4) | 13 (41.9) | 2,697 (43.5) | 49 (43.0) | 112 (48.7) | 9 (37.5) |
| Prior pregnancy (yes/no)—n (%) | 19,236 (8.6) | 8 (4.4) | 9 (8.7) | 10 (9.4) | 200 (14.3) | 1 (3.2) | 580 (9.4) | 13 (11.4) | 29 (12.6) | 0 (0.0) |
| Current pregnancy follow-up by an obstetrician—n (%) | 103,420 (46.4) | 84 (46.2) | 76 (73.8) | 64 (59.8) | 1,012 (72.4) | 18 (58.1) | 2,938 (47.3) | 91 (79.8) | 134 (58.3) | 19 (79.2) |
| High-dose folic acid exposure prior to or during pregnancy—n (%) | 8,008 (3.6) | 12 (6.6) | 24 (23.3) | 15 (14.0) | 248 (17.7) | 6 (19.4) | 403 (6.5) | 11 (9.7) | 27 (11.7) | 2 (8.3) |

Note: The total number of pregnancies exposed to at least one study medications during pregnancy is equal to 8,213.
<sup>1</sup>Heparin, dalteparin, enoxaparin and tinzaparin.
<sup>2</sup>Beta-1A, beta-1B, and alfa-2B interferons.
<sup>3</sup>Indinavir, lopinavir/ritonavir, raltegravir and saquinavir.
<sup>4</sup>Angiotensin-receptor blockers (ARB): Losartan, losartan/HCTZ, telmisartan, telmisartan/HCTZ.
<sup>5</sup>Urinary tract infection.
<sup>6</sup>Human immunodeficiency viruses.
<sup>7</sup>Low birth weight is defined as birthweight <2500 grams.
<sup>8</sup>Small for gestational age is defined as birthweight below the 10th percentile for newborns of the same gestational age and same sex.

https://doi.org/10.1371/journal.pone.0251746.t001
| Study medication exposures (any time during pregnancy): | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------------------------------------------------------|------------------|---------------------|
| Chloroquine 1.07 (0.61–1.88) | 1.10 (0.62–1.92) |
| Hydroxychloroquine 2.07 (1.16–3.70) | 1.29 (0.67–2.50) |
| Dexamethasone 2.43 (1.41–4.19) | 1.92 (1.11–3.33) |
| Anti-thrombotics 1.95 (1.64–2.33) | 1.58 (1.31–1.91) |
| Multiple sclerosis medications N.A. | N.A. | N.A. |
| Azithromycin 1.16 (1.05–1.28) | 1.05 (0.95–1.15) |
| HIV medications 3.05 (1.85–5.01) | 2.04 (1.01–4.11) |
| Oseltamivir 0.71 (0.38–1.31) | 0.63 (0.34–1.17) |
| ARB 1.23 (0.26–5.82) | 0.70 (0.15–3.29) |
| Indications for study medication exposures (during pregnancy): | Crude OR (95% CI) | Adjusted OR (95% CI) |
| Malaria 1.43 (0.70–2.90) | 1.35 (0.66–2.75) |
| Lupus 2.28 (1.50–3.47) | 1.67 (1.05–2.64) |
| Arthritis 1.01 (0.75–1.35) | 0.86 (0.65–1.15) |
| Respiratory track infections 1.01 (0.98–1.05) | 0.97 (0.93–1.00) |
| Sexual transmitted diseases/Urinary tract infections 1.15 (1.08–1.22) | 1.07 (1.00–1.14) |
| Behcet’s disease N.A. | N.A. | N.A. |
| Thrombosis 1.50 (1.24–1.81) | 1.13 (0.92–1.38) |
| Skin disorders 1.15 (0.91–1.45) | 1.10 (0.87–1.40) |
| Endocrine disorders 1.72 (1.02–2.88) | 1.37 (0.80–2.34) |
| Gastrointestinal diseases 1.49 (1.24–1.79) | 1.35 (1.12–1.63) |
| Other hematologic diseases 1.79 (1.37–2.34) | 1.60 (1.23–2.08) |
| Ankylosing spondylitis 1.21 (0.49–2.96) | 1.00 (0.41–2.47) |
| Brain tumor 1.64 (0.72–3.74) | 1.41 (0.63–3.16) |
| Human immunodeficiency virus 2.08 (1.46–2.96) | 1.35 (0.82–2.22) |
| Hepatitis 1.55 (1.06–2.27) | 1.11 (0.75–1.63) |
| Multiple sclerosis 1.21 (0.80–1.85) | 1.04 (0.68–1.57) |
| Hypertension 2.48 (2.30–2.66) | 2.47 (2.25–2.71) |
| Influenza 1.05 (0.96–1.16) | 1.03 (0.94–1.13) |
| Sociodemographic variables (at the beginning of pregnancy): | | |
| Maternal age (years) | | |
| Less than 35 Ref. | Ref. |
| 35–39 1.11 (1.06–1.17) | 1.12 (1.06–1.17) |
| 40 or more 1.36 (1.25–1.51) | 1.33 (1.21–1.46) |
| Welfare recipients 1.47 (1.42–1.53) | 1.37 (1.31–1.42) |
| Urban dweller 1.00 (0.96–1.05) | 0.99 (0.95–1.04) |
| Maternal comorbidities in the year prior to the 1 day of gestation or during pregnancy | | |
| Diabetes 1.81 (1.66–1.99) | 1.53 (1.39–1.68) |
| Asthma 1.20 (1.15–1.26) | 1.06 (1.00–1.11) |
| Thyroid disorders 1.07 (0.99–1.16) | 0.98 (0.90–1.06) |
| Tobacco dependence 1.78 (1.65–1.92) | 1.50 (1.38–1.62) |

(Continued)
Table 2. (Continued)

|                                      | Crude OR (95% CI)          | Adjusted\(^1\) OR (95% CI) |
|--------------------------------------|---------------------------|-----------------------------|
| Alcohol dependence                   | 1.95 (1.59–2.40)          | 1.06 (0.85–1.32)            |
| Other drug dependence                | 2.44 (2.17–2.75)          | 1.79 (1.58–2.03)            |
| Number of general practitioner visits (in the 12 months before pregnancy): |                          |                             |
| 0                                    | Ref.                      | Ref.                        |
| 1                                    | 1.02 (0.96–1.08)          | 1.02 (0.96–1.08)            |
| 2–4                                  | 1.04 (0.99–1.09)          | 1.00 (0.95–1.05)            |
| ≥5                                   | 1.24 (1.18–1.29)          | 1.05 (1.00–1.11)            |
| Number of specialist visits (in the 12 months before pregnancy): |                          |                             |
| 0                                    | Ref.                      | Ref.                        |
| 1–2                                  | 1.03 (0.99–1.08)          | 1.03 (0.99–1.08)            |
| ≥3                                   | 1.27 (1.18–1.29)          | 1.20 (1.14–1.25)            |
| Number of other prescribed medications (during pregnancy): |                          |                             |
| 0                                    | Ref.                      |                             |
| 1–2                                  | 1.03 (0.99–1.07)          | 0.97 (0.94–1.01)            |
| ≥3                                   | 1.27 (1.22–1.32)          | 1.03 (0.98–1.08)            |
| Hospitalization/Emergency Department visit (during pregnancy) | 1.20 (1.16–1.25) | 1.02 (0.97–1.06) |
| Current pregnancy follow-up by an obstetrician | 0.82 (0.79–0.84) | 0.78 (0.75–0.81) |
| Prior pregnancy (yes/no)             | 1.12 (1.06–1.18)          | 0.98 (0.92–1.04)            |
| High dose folic acid exposure prior to or during pregnancy | 1.36 (1.26–1.47) | 1.16 (1.07–1.26) |
| Study medication exposures (any time during pregnancy): |                          |                             |
| Chloroquine                          | 1.09 (0.59–2.02)          | 1.11 (0.59–2.08)            |
| Hydroxychloroquine                   | 2.61 (1.44–4.72)          | 1.22 (0.57–2.62)            |
| Dexamethasone                        | 1.93 (1.01–3.70)          | 1.60 (0.82–3.11)            |
| Anti-thrombotics\(^2\)               | 2.15 (1.78–2.58)          | 1.72 (1.41–2.11)            |
| Multiple sclerosis medications\(^3\) | N. A.                     | N. A.                       |
| Azithromycin                         | 1.24 (1.12–1.38)          | 1.10 (0.98–1.22)            |
| HIV medications\(^4\)               | 4.25 (2.62–6.87)          | 2.48 (1.25–4.90)            |
| Oseltamivir                          | 1.55 (0.98–2.47)          | 1.38 (0.87–2.21)            |
| ARBs\(^5\)                           | 2.80 (0.86–9.10)          | 1.48 (0.46–4.73)            |
| Indications for study medication exposures (during pregnancy): |                          |                             |
| Malaria                              | 1.05 (0.56–1.98)          | 1.09 (0.44–2.70)            |
| Lupus                                | 2.78 (1.95–3.96)          | 2.36 (1.43–3.90)            |
| Arthritis                            | 1.05 (0.83–1.32)          | 0.99 (0.74–1.33)            |
| Respiratory track infections         | 0.95 (0.93–0.98)          | 0.93 (0.89–0.97)            |
| Sexual transmitted diseases/Urinary track infections | 1.03 (0.98–1.09) | 1.05 (0.98–1.12) |
| Thrombosis                           | 1.25 (1.05–1.48)          | 1.05 (0.84–1.33)            |
| Skin disorders                       | 0.90 (0.73–1.11)          | 1.03 (0.78–1.36)            |
| Endocrine disorders                  | 1.42 (0.89–2.25)          | 1.55 (0.88–2.72)            |
| Gastrointestinal diseases            | 1.23 (1.04–1.45)          | 1.25 (1.00–1.55)            |
| Other hematologic diseases           | 1.23 (0.95–1.60)          | 1.71 (1.29–2.26)            |
| Ankylosing spondylitis               | 0.93 (0.37–2.34)          | 1.01 (0.38–2.68)            |
| Brain tumor                          | 0.80 (0.33–1.95)          | 0.52 (0.14–1.97)            |
| Human immunodeficiency virus         | 1.98 (1.46–2.69)          | 1.58 (0.96–2.59)            |
| Hepatitis                            | 2.06 (1.56–2.73)          | 1.16 (0.76–1.77)            |
| Multiple sclerosis                   | 1.53 (1.12–2.09)          | 1.34 (0.86–2.10)            |

(Continued)
Table 2. (Continued)

|                                | Crude OR (95% CI) | Adjusted\(^1\) OR (95% CI) |
|--------------------------------|------------------|---------------------------|
| Hypertension                   | 1.37 (1.27–1.48) | 3.09 (2.79–3.41)          |
| Influenza                      | 1.02 (0.95–1.11) | 0.98 (0.88–1.10)          |

**Sociodemographic variables (at the beginning of pregnancy):**

**Maternal age (years):**

| Category                | Crude OR (95% CI) | Adjusted\(^1\) OR (95% CI) |
|-------------------------|-------------------|-----------------------------|
| Less than 35            | Ref.              | Ref.                        |
| 35–39                   | 1.10 (1.04–1.16)  | 1.11 (1.04–1.17)            |
| 40 or more              | 1.45 (1.31–1.60)  | 1.39 (1.26–1.54)            |
| Welfare recipients      | 1.62 (1.55–1.69)  | 1.48 (1.41–1.54)            |
| Urban dweller           | 1.01 (0.96–1.06)  | 0.99 (0.94–1.04)            |

**Maternal comorbidities in the year prior to the first day of pregnancy or during pregnancy:**

| Condition                | Crude OR (95% CI) | Adjusted\(^1\) OR (95% CI) |
|--------------------------|-------------------|-----------------------------|
| Diabetes                 | 1.27 (1.13–1.42)  | 1.04 (0.92–1.17)            |
| Asthma                   | 1.35 (1.28–1.43)  | 1.19 (1.13–1.26)            |
| Thyroid disorders        | 1.02 (0.93–1.12)  | 0.96 (0.88–1.06)            |
| Tobacco dependence       | 2.49 (2.30–2.69)  | 2.06 (1.90–2.23)            |
| Alcohol dependence       | 2.64 (2.16–3.23)  | 1.17 (0.93–1.46)            |
| Other drug dependence    | 3.00 (2.66–3.39)  | 1.99 (1.74–2.28)            |

**Number of general practitioner visits (in the 12 months before pregnancy):**

| Category | Crude OR (95% CI) | Adjusted\(^1\) OR (95% CI) |
|----------|-------------------|-----------------------------|
| 0        | Ref.              | Ref.                        |
| 1        | 0.97 (0.91–1.04)  | 0.99 (0.93–1.06)            |
| 2–4      | 1.01 (0.96–1.07)  | 1.00 (0.94–1.06)            |
| ≥ 5      | 1.20 (1.14–1.26)  | 1.06 (1.00–1.13)            |

**Number of specialist visits (in the 12 months before pregnancy):**

| Category | Crude OR (95% CI) | Adjusted\(^1\) OR (95% CI) |
|----------|-------------------|-----------------------------|
| 0        | Ref.              | Ref.                        |
| 1–2      | 0.99 (0.94–1.04)  | 0.99 (0.94–1.04)            |
| ≥ 3      | 1.18 (1.13–1.23)  | 1.11 (1.05–1.17)            |

**Number of other prescribed medications (during pregnancy):**

| Category                | Crude OR (95% CI) | Adjusted\(^1\) OR (95% CI) |
|-------------------------|-------------------|-----------------------------|
| 0                       | Ref.              | Ref.                        |
| 1–2                     | 1.05 (1.01–1.10)  | 0.98 (0.94–1.03)            |
| ≥ 3                     | 1.26 (1.20–1.32)  | 0.99 (0.94–1.04)            |

**Hospitalization/Emergency Department visit (during pregnancy):**

| Category                | Crude OR (95% CI) | Adjusted\(^1\) OR (95% CI) |
|-------------------------|-------------------|-----------------------------|
| Current pregnancy follow-up by an obstetrician | 0.87 (0.84–0.91) | 0.86 (0.82–0.89) |
| Prior pregnancy (yes/no) | 1.12 (1.05–1.19)  | 1.01 (0.95–1.08)            |

**High dose folic acid exposure prior to or during pregnancy**

| Category                | Crude OR (95% CI) | Adjusted\(^1\) OR (95% CI) |
|-------------------------|-------------------|-----------------------------|
| Study medication exposures (any time during pregnancy):**

| Medication                      | Crude OR (95% CI) | Adjusted\(^1\) OR (95% CI) |
|---------------------------------|-------------------|-----------------------------|
| Chloroquine                     | 0.70 (0.40–1.21)  | 0.70 (0.40–1.24)            |
| Hydroxychloroquine              | 1.61 (0.90–2.87)  | 0.86 (0.42–1.75)            |
| Dexamethasone                   | 1.01 (0.56–1.83)  | 0.96 (0.52–1.77)            |
| Anti-thrombosis\(^2\)           | 1.31 (1.11–1.55)  | 1.20 (1.00–1.44)            |
| Multiple sclerosis medications\(^3\) | 0.98 (0.27–3.57)  | 0.66 (0.19–2.37)            |
| Azithromycin                    | 1.11 (1.02–1.20)  | 1.04 (0.95–1.12)            |
| HIV medications\(^4\)          | 3.34 (2.19–5.10)  | 2.61 (1.51–4.51)            |
| Oseltamivir                     | 1.21 (0.81–1.80)  | 1.13 (0.76–1.67)            |
| ARB\(^5\)                      | 0.91 (0.23–3.55)  | 0.84 (0.22–3.21)            |

**Indications for study medication exposures (during pregnancy):**

| Indication                  | Crude OR (95% CI) | Adjusted\(^1\) OR (95% CI) |
|-----------------------------|-------------------|-----------------------------|
| Malaria                     | 1.05 (0.56–1.98)  | 1.03 (0.55–1.93)            |
| Lupus                       | 2.78 (1.95–3.96)  | 2.91 (1.95–4.35)            |

(Continued)
Table 2. (Continued)

| Condition/Comorbidity | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------|------------------|----------------------|
| Arthritis             | 1.05 (0.83–1.32) | 1.04 (0.82–1.32)     |
| Respiratory track infections | 0.95 (0.93–0.98) | 0.93 (0.90–0.97)     |
| Sexual transmitted disease/Urinary track infections | 1.03 (0.98–1.09) | 1.02 (0.97–1.07)     |
| Behcet’s disease      | 3.18 (0.35–28.66) | 3.91 (0.46–33.44)    |
| Thrombosis            | 1.25 (1.05–1.48) | 1.16 (0.97–1.39)     |
| Skin disorders        | 0.90 (0.73–1.11) | 0.90 (0.73–1.11)     |
| Endocrine disorders   | 1.42 (0.89–2.25) | 1.45 (0.91–2.31)     |
| Gastrointestinal diseases | 1.23 (1.04–1.45) | 1.22 (1.03–1.44)     |
| Other hematologic diseases | 1.23 (0.95–1.60) | 1.19 (0.92–1.55)     |
| Ankylosing spondylitis | 0.93 (0.37–2.34) | 0.93 (0.39–2.26)     |
| Brain tumor           | 0.80 (0.33–1.95) | 0.80 (0.33–1.95)     |
| Human immunodeficiency virus | 1.98 (1.46–2.69) | 1.25 (0.83–1.89)     |
| Hepatitis             | 2.06 (1.56–2.73) | 1.69 (1.26–2.26)     |
| Multiple sclerosis    | 1.53 (1.12–2.09) | 1.60 (1.16–2.20)     |
| Hypertension          | 1.37 (1.27–1.48) | 1.52 (1.39–1.66)     |
| Influenza             | 1.02 (0.95–1.11) | 1.01 (0.93–1.09)     |

Sociodemographic variables (at the beginning of pregnancy):

| Variable                          | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------------------|------------------|----------------------|
| Maternal age (years)              |                  |                      |
| Less than 35                      | Ref.             | Ref.                 |
| 35–39                             | 0.95 (0.91–0.99) | 0.96 (0.92–1.01)     |
| 40 or more                        | 1.06 (0.97–1.15) | 1.06 (0.97–1.15)     |
| Welfare recipients                | 1.36 (1.31–1.40) | 1.29 (1.25–1.33)     |
| Urban dweller                     | 1.01 (0.98–1.05) | 1.00 (0.96–1.04)     |

Maternal comorbidities in the year prior to the first day of gestation or during pregnancy:

| Condition                          | Crude OR (95% CI) | Adjusted OR (95% CI) |
|------------------------------------|------------------|----------------------|
| Diabetes                           | 0.81 (0.73–0.89) | 0.80 (0.71–0.88)     |
| Asthma                             | 1.24 (1.19–1.29) | 1.19 (1.14–1.24)     |
| Thyroid disorders                  | 0.92 (0.86–0.99) | 0.95 (0.88–1.02)     |
| Tobacco dependence                 | 2.03 (1.90–2.16) | 1.83 (1.71–1.96)     |
| Alcohol dependence                 | 1.96 (1.65–2.33) | 1.15 (0.96–1.38)     |
| Other drug dependence              | 2.15 (1.93–2.39) | 1.64 (1.47–1.84)     |

Number of general practitioner visits (in the year before pregnancy):

| Visits | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------|------------------|----------------------|
| 0      | Ref.             | Ref.                 |
| 1      | 0.97 (0.93–1.02) | 1.00 (0.95–1.04)     |
| 2–4    | 0.95 (0.92–0.99) | 0.98 (0.94–1.02)     |
| ≥ 5    | 1.01 (0.97–1.05) | 1.03 (0.99–1.08)     |

Number of specialist visits (in the year before pregnancy):

| Visits | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------|------------------|----------------------|
| 0      | Ref.             | Ref.                 |
| 1–2    | 0.93 (0.90–0.96) | 0.93 (0.90–0.96)     |
| ≥ 3    | 0.89 (0.86–0.92) | 0.88 (0.85–0.91)     |

Number of other prescribed medications (during pregnancy):

| Visits | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------|------------------|----------------------|
| 0      | Ref.             | Ref.                 |
| 1–2    | 1.04 (1.01–1.08) | 1.01 (0.98–1.05)     |
| ≥ 3    | 1.09 (1.05–1.13) | 0.99 (0.95–1.03)     |

Hospitalization/Emergency Department visit (during pregnancy)

| Visits | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------|------------------|----------------------|
| 0      | Ref.             | Ref.                 |
| 1–2    | 0.96 (0.94–0.99) | 0.96 (0.92–0.99)     |
| ≥ 3    | 0.98 (0.95–1.00) | 1.02 (0.99–1.05)     |

(Continued)
Table 2. (Continued)

| Study medication exposures (in the first trimester of pregnancy): | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------------------------------------|-----------------|-----------------|
| Chloroquine                          | 0.73 (0.42–1.25) | 0.70 (0.41–1.21) |
| Hydroxychloroquine                   | 1.55 (0.92–2.63) | 1.15 (0.65–2.04) |
| Dexamethasone                        | 2.00 (1.23–3.25) | 1.66 (1.02–2.69) |
| Anti-thrombotics                     | 1.35 (1.15–1.59) | 1.02 (0.86–1.21) |
| Multiple sclerosis medications³     | 0.58 (0.14–2.36) | 0.61 (0.14–2.73) |
| Azithromycin                         | 1.18 (1.10–1.28) | 1.10 (1.02–1.19) |
| HIV medications³                     | 1.41 (0.82–2.44) | 0.90 (0.47–1.74) |
| Oseltamivir                          | 1.24 (0.84–1.84) | 1.13 (0.77–1.68) |
| ARB³                                 | 1.74 (0.62–4.85) | 1.25 (0.45–3.53) |

Indications for study medication exposures:

| Indications                          | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------------------------------------|-----------------|-----------------|
| Malaria                              | 1.11 (0.59–2.08) | 1.04 (0.55–1.94) |
| Lupus                                | 1.45 (0.98–2.15) | 1.19 (0.78–1.81) |
| Arthritis                            | 1.11 (0.89–1.38) | 1.01 (0.81–1.27) |
| Respiratory track infections         | 1.00 (0.97–1.03) | 0.96 (0.93–0.99) |
| Sexual transmitted disease/Urinary track infections | 1.04 (0.99–1.10) | 0.98 (0.94–1.04) |
| Behcet’s disease                     | N.A.            | N.A.            |
| Thrombosis                           | 1.58 (1.36–1.84) | 1.39 (1.18–1.62) |
| Skin disorders                       | 1.10 (0.91–1.34) | 1.06 (0.88–1.29) |
| Endocrine disorders                  | 1.29 (0.81–2.06) | 1.08 (0.68–1.73) |
| Gastrointestinal diseases            | 1.17 (0.99–1.38) | 1.09 (0.92–1.28) |
| Other hematologic diseases           | 1.27 (1.00–1.63) | 1.16 (0.91–1.49) |
| Ankylosing spondylitis               | 1.15 (0.54–2.44) | 1.07 (0.50–2.31) |
| Brain tumor                          | 1.18 (0.55–2.53) | 1.10 (0.52–2.34) |
| Human immunodeficiency virus         | 1.59 (1.16–2.17) | 1.38 (0.95–2.00) |
| Hepatitis                            | 1.29 (0.92–1.79) | 1.10 (0.79–1.54) |
| Multiple sclerosis                   | 0.83 (0.57–1.22) | 0.80 (0.54–1.20) |
| Hypertension                         | 1.47 (1.37–1.58) | 1.40 (1.28–1.52) |
| Influenza                            | 0.92 (0.85–1.00) | 0.90 (0.83–0.97) |

Sociodemographic variables (at the beginning of pregnancy):

| Sociodemographic variables (at the beginning of pregnancy): | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------------------------------------|-----------------|-----------------|
| Maternal age (years)                 |                 |                 |
| Less than 35                         | Ref.            | Ref.            |
| 35–39                                | 1.01 (0.97–1.05) | 0.97 (0.93–1.01) |
| 40 or more                           | 1.06 (0.97–1.15) | 0.98 (0.91–1.07) |
| Welfare recipients                   | 1.06 (1.02–1.09) | 1.00 (0.97–1.03) |
| Urban dweller                        | 1.10 (1.06–1.14) | 1.08 (1.04–1.12) |

Maternal comorbidities in the year prior to the first day of pregnancy or during pregnancy:

| Maternal comorbidities in the year prior to the first day of pregnancy or during pregnancy: | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------------------------------------|-----------------|-----------------|
| Diabetes                             | 1.50 (1.39–1.63) | 1.28 (1.18–1.38) |
| Asthma                               | 1.15 (1.11–1.20) | 1.08 (1.04–1.13) |
| Thyroid disorders                    | 1.20 (1.13–1.28) | 1.12 (1.05–1.19) |
| Tobacco dependence                   | 1.26 (1.17–1.35) | 1.20 (1.12–1.30) |
| Alcohol dependence                   | 1.22 (1.00–1.49) | 0.95 (0.77–1.16) |
| Other drug dependence                | 1.48 (1.32–1.67) | 1.34 (1.19–1.51) |

(Continued)
Discussion

Using the population-based Quebec Pregnancy Cohort, we quantified the risk of adverse perinatal outcomes associated with available medications presently considered as COVID-19 treatments. Indeed, after adjusting for potential confounders including current indications for use, and concomitant COVID-19 potential therapeutic use, we found that anti-thrombotics, mostly heparins, and HIV medication use during pregnancy were associated with the risk of prematurity, LBW and SGA. Dexamethasone was associated with increasing risks of prematurity and MCM; and azithromycin was associated with the risk of MCM.

This study adjusted for all known and measurable potential confounding variables and estimates are comparable given that they emerge from the same source population, health insurance coverage, and access to care.

Our results on dexamethasone are consistent with the literature with regards to prematurity [23,24]. Palmsten et al. [24] showed that oral corticosteroid use during pregnancy was associated with a doubling of the risk of preterm birth in women with rheumatoid arthritis recruited within teratogen information services (MotherToBaby). Early pregnancy corticosteroid use has also been associated with increased risk of MCM [15–20] similar to what we have shown.
Table 3. Organ-specific malformations stratified by first-trimester exposures to the study medications.

| Major congenital malformation by organ system | Non exposed to any of the study drugs | Chloroquine | Hydroxychloroquine | Dexamethasone | Anti-thrombotics<sup>1</sup> | Multiple sclerosis medications<sup>2</sup> | Azithromycin | HIV medications<sup>3</sup> | Oseltamivir | ARB<sup>4</sup> |
|---------------------------------------------|-------------------------------------|-------------|-------------------|--------------|----------------|-------------------|-------------|----------------|-----------|---------|
| Study medication exposures during the first trimester of pregnancy, n = 8,213 | n = 222,862 | n = 182 | n = 103 | n = 1,398 | n = 31 | n = 6,206 | n = 114 | n = 230 | n = 24 |
| Nervous system—n (%) | 1,292 (0.6) | 2 (1.1) | 2 (1.9) | 1 (0.9) | 17 (1.2) | 0 (0.0) | 43 (0.7) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Eye, ear, face—n (%) | 1,023 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 12 (0.9) | 0 (0.0) | 29 (0.5) | 0 (0.0) | 2 (0.9) | 0 (0.0) |
| Circulatory system—n (%) | 4,924 (2.2) | 3 (1.7) | 5 (4.9) | 6 (5.6) | 55 (3.9) | 0 (0.0) | 157 (2.5) | 4 (3.5) | 5 (2.2) | 1 (4.2) |
| Respiratory system—n (%) | 1,117 (0.5) | 0 (0.0) | 0 (0.0) | 2 (1.9) | 6 (0.4) | 0 (0.0) | 35 (0.6) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Orofacial, clefts—n (%) | 337 (0.2) | 1 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 16 (0.3) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Digestive system—n (%) | 1,598 (0.7) | 0 (0.0) | 2 (1.9) | 3 (2.8) | 17 (1.2) | 0 (0.0) | 61 (1.0) | 1 (0.9) | 3 (1.3) | 1 (4.2) |
| Genital system—n (%) | 1,707 (0.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 12 (0.9) | 0 (0.0) | 51 (0.8) | 0 (0.0) | 0 (0.0) | 1 (4.2) |
| Urinary system—n (%) | 1,878 (0.8) | 0 (0.0) | 0 (0.0) | 1 (0.9) | 14 (1.0) | 0 (0.0) | 65 (1.1) | 2 (1.8) | 7 (3.0) | 0 (0.0) |
| Musculoskeletal system—n (%) | 10,029 (4.5) | 7 (3.9) | 8 (7.8) | 5 (4.7) | 68 (4.9) | 1 (3.2) | 336 (5.4) | 9 (7.9) | 8 (3.5) | 0 (0.0) |

<sup>1</sup>Heparin, dalteparin, enoxaparin and tinzaparin.
<sup>2</sup>Beta-1A, beta-1B, and alfa-2B interferons.
<sup>3</sup>Indinavir, lopinavir/ritonavir, raltegravir and saquinavir.
<sup>4</sup>Angiotensin-receptor blockers (ARB): Losartan, losartan/HCTZ, telmisartan, telmisartan/HCTZ.

https://doi.org/10.1371/journal.pone.0251746.t003
We found no orofacial defect with dexamethasone use as was reported in more recent pregnancy studies [21,22]. Our findings on anti-thrombotics (mostly heparins) use and pregnancy are different from what has been published recently. The increased prevalence of adverse fetal/infant outcomes including death, prematurity and MCM have been reported following heparin use [72]. However, in another more recent study performed by Shlomol et al. [28], no such associations were found within an Israeli cohort of pregnant women. While heparin does not appear to cross the placenta, it may affect embryo and fetal development through interactions with the trophoblast and placental vasculature [73]. Differences between our findings and those from Shlomol et al. [28] could be partly explained by their lack of adjustment for potential confounders such as gestational hypertension and diabetes, indications for heparin use, and lifestyles such as tobacco and alcohol use.

Our findings on the association between indinavir, lopinavir/ritonavir, raltegravir and saquinavir (HIV drugs) use during pregnancy and the risk of prematurity, LBW and SGA [51]; and on chloroquine, and hydroxychloroquine with regards to prematurity, LBW or MCM are also consistent with the literature [46].

We found that azithromycin use was increasing the risk of MCM. A recent population-based cohort study using data from the Clinical Practice Research Datalink in the United Kingdom has shown that use of macrolide antibiotics, including erythromycin, clarithromycin, or azithromycin, during pregnancy was associated with an increased risk of overall major congenital malformations in children [74]. Similarly, a population based cohort study using data from the Swedish Medical Birth Register has shown an association between early pregnancy erythromycin use and infant cardiovascular defects [75].

**Strengths and potential limitations**

Study strengths include the use of population-based prospective pregnancy cohort with linkage of data at the individual level, which minimized selection and recall biases; this also allowed for analyses on a large number of pregnancies with detailed information regarding exposure, outcomes, and potential confounders. The fact that all potential available medications for COVID-19 treatments were studied within a unique and single population allowed for comparative safety assessments. QPC data on filled prescriptions [70], gestational age [67], birth weight [67], and MCM [67] have all been validated. Adjustment on all known and measurable potential confounders for adverse pregnancy outcomes was made, including maternal comorbidities, indications for medication uses, lifestyles including smoking, alcohol, illicit drug use, and high dose folic acid intake; adjustment was also made on health services utilization, which is considered a proxy for severity of diseases.

One potential limitation is missing information on over-the-counter (OTC) medication use, and use of medications during in-hospital deliveries. Other than for ibuprofen and acetaminophen use and non-prescribed folic acid use, all other medications will be prescribed. It is possible that some women took folic acid OTC. However, this would lead to non-differential misclassification as it is unlikely that those exposed to the study medications would differ in terms of prevalence of folic acid OTC compared to those who were not exposed. Since the databases only include pregnant women insured by the Prescription Drug Insurance program, generalizability of results to those insured by private drug insurance could be affected. However, validation studies have shown that publicly insured pregnant women have similar characteristics and co-morbidities than those who have private medication insurance [76]. We considered filled prescriptions and not actual intake, but Zhao et al. [70] have shown that prescription filling data in the QPC were valid when compared to maternal report. Although
health services utilization was adjusted for and considered a proxy for disease severity, residual confounding by severity of disease could remain. Our estimates could be slightly biased upwards since we only considered deliveries in our analyses as is done in the majority of studies on medications and pregnancy. Finally, the MCM prevalence of 10.3% is higher than what is routinely reported (3–5%) [77]. This could be partly explained by the Founders’ effect in the province of Quebec. [78,79]. It can also be partly explained by the fact that we have included all pregnancies between 1998 and 2015, and we have required that all pregnant women and children be insured by the RAMQ public medication insurance program in order to fully measure medication exposures during pregnancy (we only have medication data on those insured by the RAMQ public medication insurance program). This, in addition to the Founders’ effect, could explain the MCM prevalence. Although our baseline prevalence of MCMs is high, it does not differ among our compared groups, and therefore does not invalidate our findings. This, however, could limit the generalizability of our results.

Conclusions
Using the population-based Quebec Pregnancy Cohort, gestational exposure to dexamethasone was associated with an increased risk of prematurity and MCM; azithromycin exposure was associated with the risk of MCM, and exposure to anti-thrombotics (mostly heparins), and indinavir, lopinavir/ritonavir, raltegravir and saquinavir (HIV drugs) use during pregnancy were associated with increased risks of prematurity, LBW and SGA. Although these available medications are being considered as treatments for COVID-19, caution is warranted in pregnancy.

Supporting information
S1 Fig. Quebec Pregnancy Cohort database linkage.
(DOCX)
S2 Fig. Quebec Pregnancy Cohort outcomes and babies.
(DOCX)
S1 Table. List of known fetotoxic prescribed medications excluded.
(DOCX)
S2 Table. ICD-9 and ICD-10 diagnostic codes of major congenital malformations.
(DOCX)
S3 Table. List of diagnostic codes (ICD-9 and ICD-10) and medications used for the covariates.
(DOCX)

Author Contributions
Conceptualization: Anick Bérard, Odile Sheehy, Jin-Ping Zhao, Evelyne Vinet, Caroline Quach, Behrouz Kassai, Sasha Bernatsky.
Data curation: Anick Bérard, Odile Sheehy.
Formal analysis: Anick Bérard, Odile Sheehy.
Funding acquisition: Anick Bérard.
Investigation: Anick Bérard, Odile Sheehy, Jin-Ping Zhao, Evelyne Vinet, Caroline Quach, Behrouz Kassai, Sasha Bernatsky.
Methodology: Anick Bérand, Odile Sheehy, Jin-Ping Zhao, Evelyne Vinet, Caroline Quach, Behrouz Kassai, Sasha Bernatsky.

Project administration: Anick Bérand.

Resources: Anick Bérand.

Software: Anick Bérand, Odile Sheehy.

Supervision: Anick Bérand.

Validation: Anick Bérand, Odile Sheehy, Jin-Ping Zhao, Evelyne Vinet, Caroline Quach, Behrouz Kassai, Sasha Bernatsky.

Visualization: Anick Bérand, Odile Sheehy, Jin-Ping Zhao, Evelyne Vinet, Caroline Quach, Behrouz Kassai, Sasha Bernatsky.

Writing – original draft: Anick Bérand, Jin-Ping Zhao.

Writing – review & editing: Anick Bérand, Odile Sheehy, Jin-Ping Zhao, Evelyne Vinet, Caroline Quach, Behrouz Kassai, Sasha Bernatsky.

References

1. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol 2010; 63:425–33. https://doi.org/10.1111/j.1600-0897.2010.00836.x PMID: 20367629

2. Ramsey PS, Ramin KD. Pneumonia in pregnancy. Obstet Gynecol Clin North Am 2001; 28:553–69. https://doi.org/10.1016/s0889-8545(05)70217-5 PMID: 11512500

3. Rasmussen SA, Kissin DM, Yeung LF, MacFarlane K, Chu SY, Turcios-Ruiz RM, et al. Preparing for influenza after 2009 H1N1: special considerations for pregnant women and newborns. Am J Obstet Gynecol 2011; 204:S13–20. https://doi.org/10.1016/j.ajog.2011.01.048 PMID: 21333967

4. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano L, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status—United States, January 22–June 7, 2020. MMWR Morb Mortal Wkly Rep 2020; 69:769–73. https://doi.org/10.15585/mmwr.mm6925a1 PMID: 32584795

5. COVID WWGo. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection. Ultrasound Obstet Gynecol 2021; 57:232–41. https://doi.org/10.1002/uog.23107 PMID: 32926494

6. https://clinicaltrials.gov/ct2/who_table.

7. Horby P, Lim WS, Emberson J, Mafham M, Bell J, Landary MJ, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. medRxiv June 22,2020. https://doi.org/10.1101/2020.06.22.20137273 preprint. PMID: 32690491

8. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. Cell Host Microbe 2020; 27:992–1000 e3. https://doi.org/10.1016/j.chom.2020.04.009 PMID: 32320677

9. Johnson RM, Vinetz JM. Dexamethasone in the management of covid-19. BMJ 2020; 370:m2648. https://doi.org/10.1136/bmj.m2648 PMID: 32620554

10. Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician’s perspective. Diabetes Metab Syndr 2020; 14:971–8. https://doi.org/10.1016/j.dsx.2020.06.054 PMID: 32610262

11. Magro G. COVID-19: Review on latest available drugs and therapies against SARS-CoV-2. Coagulation and inflammation cross-talking. Virus Res 2020; 286:198070. https://doi.org/10.1016/j.virusres.2020.198070 PMID: 32569708

12. Brown RW, Diaz R, Robson AC, Kotlevtsev YY, Mullins JJ, Kaufman MH, et al. The ontogeny of 11 beta-hydroxysteroid dehydrogenase type 2 and mineralocorticoid receptor gene expression reveal intricate control of glucocorticoid action in development. Endocrinology 1996; 137:794–7. https://doi.org/10.1210/endo.137.2.8593833 PMID: 8593833

13. Beltins IZ, Bayard F, Ances IG, Kowarski A, Migeon CJ. The metabolic clearance rate, blood production, interconversion and transplacental passage of cortisol and cortisone in pregnancy near term. Pediatr Res 1973; 7:509–19. https://doi.org/10.1002/0006450-197305000-00004 PMID: 4704743
14. Reinisch JM, Simon NG, Karow WG, Gandelman R. Prenatal exposure to prednisone in humans and animals retards intrauterine growth. Science 1978; 202:436–8. https://doi.org/10.1126/science.705336 PMID: 705336

15. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999; 86:242–4. PMID: 10482873

16. Carmichael SL, Shaw GM, Ma C, Werler MM, Rasmussen SA, Lammer EJ, National Birth Defects Prevention S. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol 2007; 197:585.e1–7; discussion 683–4, e1-7. https://doi.org/10.1016/j.ajog.2007.05.046 PMID: 18069043

17. Pradat P, Robert-Gnansia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P. Contributors to the Md. First trimester exposure to corticosteroids and oral clefts. Birth Defects Res A Clin Mol Teratol 2003; 67:968–70. https://doi.org/10.1002/bdra.10134 PMID: 14745915

18. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology 1998; 58:2–5. PMID: 9699238

19. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnissett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000; 62:385–92. PMID: 11091360

20. Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A Review of Systemic Corticosteroid Use in Pregnancy and the Risk of Select Pregnancy and Birth Outcomes. Rheum Dis Clin North Am 2017; 43:489–502. https://doi.org/10.1016/j.rdc.2017.04.013 PMID: 28711148

21. Hviid A, Molgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. CMAJ 2011; 183:796–804. https://doi.org/10.1503/cmaj.101063 PMID: 21482652

22. Skuladottir H, Wilcox AJ, Ma C, Lammer EJ, Rasmussen SA, Werler MM, et al. Corticosteroid use and risk of orofacial clefts. Birth Defects Res A Clin Mol Teratol 2014; 100:499–506. https://doi.org/10.1002/bdra.23248 PMID: 24777675

23. Norgard B, Pedersen L, Christensen LA, Sorensen HT. Therapeutic drug use in women with Crohn’s disease and birth outcomes: a Danish nationwide cohort study. Am J Gastroenterol 2007; 102:1406–13. https://doi.org/10.1111/j.1572-0241.2007.01216.x PMID: 17437503

24. Palmsten K, Bandoli G, Vazquez-Benitez G, Xi M, Johnson DL, Xu R, et al. Oral corticosteroid use during pregnancy and risk of preterm birth. Rheumatology (Oxford) 2020; 59:1262–71. https://doi.org/10.1093/rheumatology.kez405 PMID: 31566229

25. Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020; 395:1695–704. https://doi.org/10.1016/S0140-6736(20)31042-4 PMID: 32401715

26. Lee SG, Fralick M, Sholzberg M. Coagulopathy associated with COVID-19. CMAJ 2020; 192:E583. https://doi.org/10.1503/cmaj.200685 PMID: 32357997

27. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18:1094–9. https://doi.org/10.1111/jth.14817 PMID: 3220112

28. Shlomo M, Gorodischer R, Daniel S, Wiznitzer A, Matok I, Fishman B, et al. The Fetal Safety of Enoxaparin Use During Pregnancy: A Population-Based Retrospective Cohort Study. Drug Saf 2017; 40:1147–55. https://doi.org/10.1007/s40264-017-0573-7 PMID: 28733971

29. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426:450–4. https://doi.org/10.1038/ nature02145 PMID: 14647384

30. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, et al. Structural basis of receptor recognition by SARS-CoV-2. Nature 2020; 581:221–4. https://doi.org/10.1038/s41586-020-2179-y PMID: 32225175

31. Whelton PK, Carey RM. The 2017 Clinical Practice Guideline for High Blood Pressure. JAMA 2017; 318:2073–4. https://doi.org/10.1001/jama.2017.18209 PMID: 29159375

32. Furuhashi M, Moniwa N, Mita T, Fuseya T, Ishimura S, Ohno K, et al. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. Am J Hypertens 2015; 28:15–21. https://doi.org/10.1093/ajh/hpu086 PMID: 24842388

33. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur Heart J 2020; 41:1801–3. https://doi.org/10.1093/eurheartj/ehaa235 PMID: 32196087

34. Sommerstein R, Kochen MM, Messerli FH, Grani C. Coronavirus Disease 2019 (COVID-19): Do Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Have a Biphasic Effect? J Am Heart Assoc 2020; 9:e016509. https://doi.org/10.1161/JAHA.120.016509 PMID: 32233753
35. Fang L, Karakuilakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020; 8:e21. https://doi.org/10.1016/S2213-2600(20)30116-8 PMID: 3217062
36. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006; 354:2443–51. https://doi.org/10.1056/NEJMoa055202 PMID: 16760444
37. Quan A. Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. Early Hum Dev 2006; 82:23–8. https://doi.org/10.1016/j.earlhumdev.2005.11.001 PMID: 16427219
38. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers: a systematic review. Hypertension 2012; 60:444–50. https://doi.org/10.1161/HYPERTENSIONAHA.112.196352 PMID: 22753220
39. Moretti ME, Caprara D, Drehuta I, Yeung E, Cheung S, Federico L, et al. The Fetal Safety of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers. Obstet Gynecol Int 2012; 2012:658310. https://doi.org/10.1155/2012/658310 PMID: 22203847
40. Moretti ME, Caprara D, Drehuta I, Yeung E, Cheung S, Federico L, et al. The Fetal Safety of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers. Obstet Gynecol Int 2012; 2012:658310. https://doi.org/10.1155/2012/658310 PMID: 22203847
41. Cox RM, Anderson JM, Cox P. Defective embryogenesis with angiotensin II receptor antagonists in pregnancy. BJOG 2003; 110:1038. PMID: 14592593
42. Barr M. Teratogen update: angiotensin-converting enzyme inhibitors. Teratology 1994; 50:399–409. https://doi.org/10.1002/tera.1420500606 PMID: 7778045
43. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020:105949.
44. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020 Mar. 31. https://doi.org/10.1001/jama.2020.22240 PMID: 33165621
45. Meo SA, Klonof DC, Akram J. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. Eur Rev Med Pharmacol Sci 2020; 24:4539–47. https://doi.org/10.26355/eurrev_202004_21038 PMID: 32373993
46. Schrezenmeier E, Donner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol 2020; 16:155–66. https://doi.org/10.1038/s41584-020-0372-x PMID: 32034323
47. Lacroix I, Benevent J, Damase-Michel C. Chloroquine and hydroxychloroquine during pregnancy: What do we know? Therapie 2010; 75:384–5. https://doi.org/10.1022/tera.1420500606 PMID: 7778045
48. Vatansever EC, Yang K, Kratch KC, Drelich A, Cho CC, Mellot DM, et al. Targeting the SARS-CoV-2 Main Protease to Repurpose Drugs for COVID-19. bioRxiv 2020. https://doi.org/10.1101/2020.05.23.112235 PMID: 32511370
49. Powis KM, Kitch D, Ogwu A, Hughes MD, Lockman S, Leidner J, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. J Infect Dis 2011; 204:506–14. https://doi.org/10.1093/infdis/jir307 PMID: 21791651
50. Watts DH, Williams PL, Kacanek D, Griner R, Rich K, Hazra R, et al. Pediatric HIV/AIDS. Combination antiretroviral use and preterm birth. J Infect Dis 2013; 207:612–21. https://doi.org/10.1093/infdis/jits728 PMID: 23204173
51. Gagnon LH, MacGillivray J, Urquia ML, Caprara D, Murphy KE, Yudin MH. Antiretroviral therapy during pregnancy and risk of preterm birth. Eur J Obstet Gynecol Reprod Biol 2016; 201:51–5. https://doi.org/10.1016/j.ejogrb.2016.03.028 PMID: 27060543
52. Chen JY, Ribaudo HJ, Souda S, Parekh N, Ogwu A, Lockman S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. J Infect Dis 2012; 206:695–705. https://doi.org/10.1093/infdis/jis553 PMID: 23066160
55. Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? J Infect Dis 2006; 193:1195–201. https://doi.org/10.1086/503045 PMID: 16586354

56. Patel K, Shapiro DE, Brogly SB, Livingston EG, Stek AM, Bardeguez AD, et al, Group PtotIMA CT. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. J Infect Dis 2010; 201:1035–44. https://doi.org/10.1086/651232 PMID: 20196654

57. Duryea E, Nicholson F, Cooper S, Roberts S, Rogers V, McIntire D, et al. The Use of Protease Inhibitors in Pregnancy: Maternal and Fetal Considerations. Infect Dis Obstet Gynecol 2015; 2015:563727. https://doi.org/10.1155/2015/563727 PMID: 26617456

58. Slyker JA, Patterson J, Ambler G, Richardson BA, Maleche-Obimbo E, Bosire R, et al. Correlates and outcomes of preterm birth, low birth weight, and small for gestational age in HIV-exposed uninfected infants. BMC Pregnancy Childbirth 2014; 14:7. https://doi.org/10.1186/1471-2393-14-7 PMID: 24397463

59. Sibiude J, Warszawski J, Tubiana R, Dollfus C, Faye A, Rouzioux C, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? Clin Infect Dis 2012; 54:1348–60. https://doi.org/10.1093/cid/cis198 PMID: 22460969

60. Fiore S, Ferrazzi E, Newell ML, Trabattoni D, Clerici M. Protease inhibitor-associated increased risk of preterm delivery is an immunological complication of therapy. J Infect Dis 2007; 195:914–6; author reply 6–7. https://doi.org/10.1086/511983 PMID: 17299724

61. Hanna N, Bonifacio L, Weinberger B, Reddy P, Murphy S, Romero R, et al. Evidence for interleukin-10-mediated inhibition of cyclo-oxygenase-2 expression and prostaglandin production in preterm human placenta. Am J Reprod Immunol 2006; 55:19–27. https://doi.org/10.1111/j.1600-0897.2005.00342.x PMID: 16364008

62. Zash R, Makhema J, Shapiro RL. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. N Engl J Med 2018; 379:979–81. https://doi.org/10.1056/NEJMct1807653 PMID: 30037297

63. Rasi V, Cortina-Borja M, Peters H, Sconza R, Thorne C. Brief Report: Surveillance of Congenital Anomalies After Exposure to Raltegravir or Elvitegravir During Pregnancy in the United Kingdom and Ireland, 2008–2018. J Acquir Immune Defic Syndr 2019; 80:264–8. https://doi.org/10.1097/QAI.0000000000002031 PMID: 30908331

64. Blais L, Berard A, Kettani FZ, Forget A. Validity of congenital malformation diagnostic codes recorded in Quebec’s administrative databases. Pharmacoepidemiol Drug Saf 2013; 22:881–9. https://doi.org/10.1002/pds.3446 PMID: 23616437

65. tense caused by an antihypertensive agent. Br J Clin Pharmacol 1994; 38:407–12. https://doi.org/10.1111/j.1365-2125.1994.tb02934.x PMID: 7978486

66. Zhao JP, Sheehy O, Gorgui J, Berard A. Can We Rely on Pharmacy Claims Databases to Ascertain Maternal Use of Medications during Pregnancy? Birth Defects Res 2017; 109:423–31. https://doi.org/10.1002/bdra.23604 PMID: 28398706

67. Krammer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, et al. Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance S. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics 2001; 108:E35. https://doi.org/10.1542/peds.108.2.e35 PMID: 11483485

68. Ginsberg JS, Hirsh J, Turner DC, Levine MN, Burrows R. Risks to the fetus of anticoagulant therapy during pregnancy. Thromb Haemost 1989; 61:197–203. PMID: 2665171

69. Alvarez AM, Balcazar N, San Martin S, Markert UR, Cadavid AP. Modulation of antiphospholipid antibodies-induced trophoblast damage by different drugs used to prevent pregnancy morbidity associated with pregnancy.
74. Fan H, Gilbert R, O’Callaghan F, Li L. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population based cohort study. BMJ 2020; 368: m331. https://doi.org/10.1136/bmj.m331 PMID: 32075790
75. Kallen B, Danielsson BR. Fetal safety of erythromycin. An update of Swedish data. Eur J Clin Pharmacol 2014; 70:355–60. https://doi.org/10.1007/s00228-013-1624-3 PMID: 24352632
76. Berard A, Lacasse A. Validity of perinatal pharmacoepidemiologic studies using data from the RAMQ administrative database. Can J Clin Pharmacol 2009; 16:e360–9. PMID: 19553702
77. Egbe AC. Birth defects in the newborn population: race and ethnicity. Pediatr Neonatol 2015; 56:183–8. https://doi.org/10.1016/j.pedneo.2014.10.002 PMID: 25544042
78. Laberge AM. [Prevalence and distribution of genetic diseases in Quebec: impact of the past on the present]. Med Sci (Paris) 2007; 23:997–1001. https://doi.org/10.1051/medsci:20072311997 PMID: 18021714
79. Zhao JP, Sheehy O, Berard A. Regional Variations in the Prevalence of Major Congenital Malformations in Quebec: The Importance of Fetal Growth Environment. J Popul Ther Clin Pharmacol 2015; 22:e198–210. PMID: 26567551