Received: 18 November 2021 | Revised: 21 March 2022 | Accepted: 28 March 2022

DOI: 10.1002/pds.5440

BRIEF REPORT

WILEY

COVID-19 pharmacotherapy utilization patterns during pregnancy: International Registry of Coronavirus Exposure in Pregnancy

Whitney J. Westhoff[1] | Louisa H. Smith[1] | Diego F. Wyszynski[2] | Sonia Hernandez-Diaz[1]

[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

[2]Pregistry, Los Angeles, California, USA

Correspondence
Whitney J. Westhoff, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA.
Email: whitneywesthoff@hsph.harvard.edu

Funding information
Pregistry received financial support for The International Registry of Coronavirus Exposure in Pregnancy from Regeneron Pharmaceuticals, Inc. and Johnson & Johnson Services, Inc.

Abstract

Purpose: Women infected with SARS-CoV-2 during pregnancy are at increased risk of developing severe illness and experience a higher rate of preterm births than pregnant women who are not infected. The use of innovative or repurposed therapies to treat COVID-19 patients is widespread; however, there are very limited data regarding the patterns of use and safety profile of most of these therapeutics in pregnant women. We assessed the patterns of use of COVID-19 therapeutics during pregnancy using data from the International Registry of Coronavirus in Pregnancy (IRCEP).

Methods: The IRCEP is an international observational cohort study intended to assess the risk of major obstetric and neonatal outcomes among pregnant women with COVID-19. Women enrolled while pregnant or within 6 months after end of pregnancy. Follow-up for women enrolled while pregnant includes monthly online questionnaires throughout the pregnancy and, for live births, through the infant's first 90 days of life. Participants provide information on demographic characteristics, health history, COVID-19 tests and symptoms, medications, and obstetric and neonatal outcomes.

Results: A total of 5780 women with COVID-19 during pregnancy were identified from the IRCEP. Severity of COVID-19 was classified in 372 of them as severe, 3053 moderate, and 2355 mild. The most frequently reported COVID-19 therapies, other than analgesics, included azithromycin (12.8%), steroids (3.5%), interferon (2.4%), oseltamivir (2.1%), chloroquine/hydroxychloroquine (1.7%), anticoagulants (2.0%), antibodies (0.9%), and remdesivir (0.3%). Most drugs were preferentially used for severe cases. Patterns of use varied by country.

Conclusions: IRCEP participants reported use of therapeutics for COVID-19 during pregnancy for which there is little safety information. Findings on COVID-19 pharmacotherapy utilization patterns can guide future studies examining the safety of COVID-19 therapies during pregnancy.

KEYWORDS
COVID-19, COVID-19 treatment, drug utilization, pharmacoepidemiology, pregnancy

Key Points

- A total of 5780 participants from an international, observational cohort of women were identified with COVID-19 during pregnancy and reported pharmacotherapy use.
- The most frequently reported COVID-19 therapies, other than analgesics, included azithromycin, steroids, interferon, oseltamivir, chloroquine/hydroxychloroquine, and antibodies.
- COVID-19-specific medications were reported to be used more frequently among patients with severe disease than in those with lower severity. Therapy use patterns varied by country but not notably between trimesters of infection.
- IRCEP participants reported use of therapeutics for COVID-19 during pregnancy for which there is little safety information.

Plain language summary

Pregnant women infected with SARS-CoV-2 may develop severe COVID-19 and require treatment. Despite this, little is known about the patterns of use and safety of many COVID-19 medications in pregnancy. In an international study of 5780 women with COVID-19 during pregnancy, we evaluated the utilization of medications for COVID-19 in pregnancy. Therapy use patterns varied by disease severity and country, but not notably between trimesters of infection. Participants reported use of medications for COVID-19 during pregnancy for which there is little safety information.

1 | INTRODUCTION

Women infected with SARS-CoV-2 during pregnancy are at risk of developing severe illness and experience a higher rate of preterm births than pregnant women who are not infected.[1–4] Therefore, pregnant patients with symptomatic SARS-CoV-2 infection have been, and will be, treated to prevent or cure severe COVID-19.[5]

A number of therapeutics have been approved or authorized for treatment of COVID-19 in various countries, such as remdesivir, favipiravir, baricitinib, tocilizumab, and more recently casirivimab/imdevimab and sotrovimab, among others. Investigational use of repurposed medications to treat COVID-19 also remains high, with some research showing safety in pregnancy for repurposed medications based on experience with other indications.[6–9] However, there remains an overall dearth of knowledge about the usage patterns and safety profile of many of these therapeutics in pregnant women and their developing offspring.[10,11]

2 | METHODS

2.1 | Study design

The International Registry of Coronavirus Exposure in Pregnancy (IRCEP) is an international observational cohort study that includes adult women tested for SARS-CoV-2, regardless of the results, or with clinical confirmation of COVID-19 during pregnancy. Between July 2020 and June 2021, women voluntarily enrolled while pregnant or within 6 months after pregnancy end. Information about the IRCEP was available on a dedicated website (https://corona.pregistry.com/). Venues for increasing awareness included social media channels frequently visited by pregnant women (e.g., Facebook) and online parenting forums.

Women enrolled while pregnant completed short monthly online questionnaires throughout pregnancy and for 90 days after delivery for live births. Women enrolled after pregnancy completed a retrospective questionnaire covering the same information as those enrolled during pregnancy. Participants provided detailed information on COVID-19 tests, specific symptoms, date, and gestational timing of test and symptoms, and indicators of disease severity. Additional information collected includes demographics (age, race/ethnicity, country of residence, and education), pre-pregnancy body mass index, gestational age, health history, use of medications, and obstetric and neonatal outcomes. More detailed information about the IRCEP can be found elsewhere.[12]

2.2 | Study population

We included all women with symptomatic COVID-19 during pregnancy based on a positive laboratory test or clinical diagnosis. They were subsequently categorized into one of three levels of COVID-19 severity using the following criteria: (1) severe COVID-19: self-report of being admitted to the ICU, needing respirator assistance, ECMO, or ventilation, or who were hospitalized with organ failure, pneumonia, acute respiratory distress syndrome, abnormal chest X-ray or CT scan, chest pain, blue lips, or breathing difficulties; (2) moderate COVID-19: those with pneumonia, respiratory distress, or breathing difficulties without hospitalization, or who were hospitalized or reported to the ER or clinic with upper respiratory symptoms, fatigue or myalgia, a

TABLE 1 Medication utilization in participants with SARS-CoV-2 infection during pregnancy by severity

Drug	Mild ($n = 2355$)	Moderate ($n = 3053$)	Severe ($n = 372$)	Overall ($n = 5780$)
Analgesics				
Acetaminophen	731 (31.0%)	1179 (38.6%)	184 (49.5%)	2094 (36.2%)
NSAID	40 (1.7%)	115 (3.8%)	30 (8.1%)	185 (3.2%)
Aspirin	45 (1.9%)	104 (3.4%)	19 (5.1%)	168 (2.9%)
Antimalarials				
Chloroquine/hydroxychloroquine	19 (0.8%)	56 (1.8%)	24 (6.5%)	99 (1.7%)
Antivirals				
Oseltamivir	19 (0.8%)	76 (2.5%)	24 (6.5%)	119 (2.1%)
Remdesivir	0 (0.0%)	4 (0.1%)	16 (4.3%)	20 (0.3%)
Lopinavir	1 (0.0%)	4 (0.1%)	11 (3.0%)	16 (0.3%)
Ritonavir	2 (0.1%)	4 (0.1%)	6 (1.6%)	12 (0.2%)
Tenofovir	0 (0.0%)	0 (0.0%)	2 (0.5%)	2 (0.0%)
Other antiviral[a]	4 (0.2%)	13 (0.4%)	5 (1.3%)	22 (0.4%)
Biologics				
Antibodies	16 (0.7%)	23 (0.8%)	12 (3.2%)	51 (0.9%)
IL-6 inhibitor	0 (0.0%)	5 (0.2%)	6 (1.6%)	11 (0.2%)
Intravenous immune globulin	1 (0.0%)	1 (0.0%)	8 (2.2%)	10 (0.2%)
Plasma	0 (0.0%)	1 (0.0%)	7 (1.9%)	8 (0.1%)
Other COVID-19 medications				
Antibiotic (incl. azithromycin)	200 (8.5%)	575 (18.8%)	121 (32.5%)	896 (15.5%)
Azithromycin	159 (6.8%)	479 (15.7%)	102 (27.4%)	740 (12.8%)
Steroid/corticosteroid	29 (1.2%)	116 (3.8%)	57 (15.3%)	202 (3.5%)
Interferon	57 (2.4%)	65 (2.1%)	16 (4.3%)	138 (2.4%)
Antiparasitic	18 (0.8%)	35 (1.1%)	4 (1.1%)	57 (1.0%)
Dipyrone	8 (0.3%)	28 (0.9%)	0 (0.0%)	36 (0.6%)
Other supportive medications				
Cough suppressant	103 (4.4%)	229 (7.5%)	56 (15.1%)	388 (6.7%)
Anticoagulant	33 (1.4%)	48 (1.6%)	34 (9.1%)	115 (2.0%)
Antihistamine	23 (1.0%)	63 (2.1%)	2 (0.5%)	88 (1.5%)
Albuterol/inhaled asthma drug	7 (0.3%)	53 (1.7%)	8 (2.2%)	68 (1.2%)
Decongestant	15 (0.6%)	10 (0.3%)	0 (0.0%)	25 (0.4%)
Antiemetic	1 (0.0%)	14 (0.5%)	2 (0.5%)	17 (0.3%)
Topical antiseptic	7 (0.3%)	6 (0.2%)	0 (0.0%)	13 (0.2%)
Alternative therapies[b]	20 (0.8%)	14 (0.5%)	0 (0.0%)	34 (0.6%)
Vitamins/supplements	45 (1.9%)	60 (2.0%)	11 (3.0%)	116 (2.0%)
Other medication[c]	12 (0.5%)	15 (0.5%)	13 (3.5%)	40 (0.7%)

[a]Other antivirals included umifenovir, inosine pranobex, amantadine, aciclovir, influcein, rimantadine, ingavirin.
[b]Alternative therapies included aromatherapy, homeopathic treatments, and so forth.
[c]Other medications reported as SARS-CoV-2 treatments by a small number of participants included antidepressants, antiepileptic drugs, milk of magnesia, antacids, insulin, metformin, antihypertensives, opioids, and proton-pump inhibitors.

fever above 38°C, loss of taste or smell, headache, diarrhea, nausea, or vomiting; and (3) mild COVID-19: any other symptoms of lesser severity than those of moderate or severe COVID-19.

All pharmacotherapy information was collected via online self-reported surveys. Participants responded "Yes" or "No" to the question: *Did you take any medication during pregnancy to treat COVID-19?* If they chose "Yes," they were prompted to select from a menu of COVID-19 approved and authorized treatments, including repurposed medications. If they chose the option "Other," they were asked to indicate the name of the medication in a free text box. We reviewed the text fields for these "Other" medications and further classified them into therapeutic groups.

2.3 | Analyses

We describe here the pharmacologic treatments used to treat COVID-19 during pregnancy in the IRCEP. We assessed (1) COVID-19-specific medications, defined as pharmacological agents under investigation or reported to have effects against COVID-19, such as remdesivir, steroids, tocilizumab, hydroxychloroquine/chloroquine, azithromycin, and interferon-beta and (2) medications used for supportive care in patients with COVID-19, such as analgesics or antipyretics, statins, anti-infective agents (antibiotics, antifungals, and antivirals approved for other viruses), anticoagulants, inhalers/nebulizers, proton pump inhibitors, and histamine H2-receptor antagonists. We evaluated treatment patterns by COVID-19 severity and region when numbers allowed. We examined patterns of medication use by trimester among women with severe COVID-19, combining categories of drugs into antibiotics, analgesics, biologics, and antivirals due to limited numbers. Sensitivity analyses restricted the population to those with a positive COVID-19 test and those enrolled while pregnant.

3 | RESULTS

We evaluated 5780 study participants with COVID-19 during pregnancy from the IRCEP. Of those, COVID-19 was categorized as severe in 372, moderate in 3053, and mild in 2355. Among study participants overall, 1688 (29.2%), 2045 (35.4%), and 1534 (26.5%) were diagnosed during their first, second, or third trimester, respectively. The median age of the study population was 30 years, with a median pre-pregnancy BMI of 25 kg/m^2. Study participants were spread across 47 countries with a variety of ethnic and socioeconomic backgrounds.

Self-reported medications for COVID-19, including both COVID-19-specific and supportive therapies, are presented in Table 1.

3.1 | Patterns by disease severity

Use of therapies increased with disease severity for most medications (Table 1). Azithromycin use among participants with severe COVID-19 (27.4%) was markedly higher than among mild cases (6.8%), as was use of anticoagulants (9.1% severe, 1.4% mild), steroids (15.3% severe, 1.2% mild), acetaminophen (49.5% severe, 31.0% mild), and nonsteroidal anti-inflammatory drugs (8.1% severe, 1.7% mild). Antihistamines (2.1% moderate, 0.5% severe) did not follow the pattern of increased use with increase severity.

3.2 | Patterns by gestational age

The distribution of disease severity varied by trimester of infection; the frequency of participants with severe disease was higher in the third trimester (9.8%) than in the second (5.6%) and first (2.5%) trimesters. Among cases with severe COVID-19, analgesics were taken by 52.3%, 61.4%, and 48.7% of participants in their first, second, and third trimesters, respectively. Antibiotics (23.8% first, 35.1% second, 32.7% third), antivirals (11.9% first, 15.8% second, 16.7% third), and biologics (7.1% first trimester, 13.2% second trimester, 10.7% third

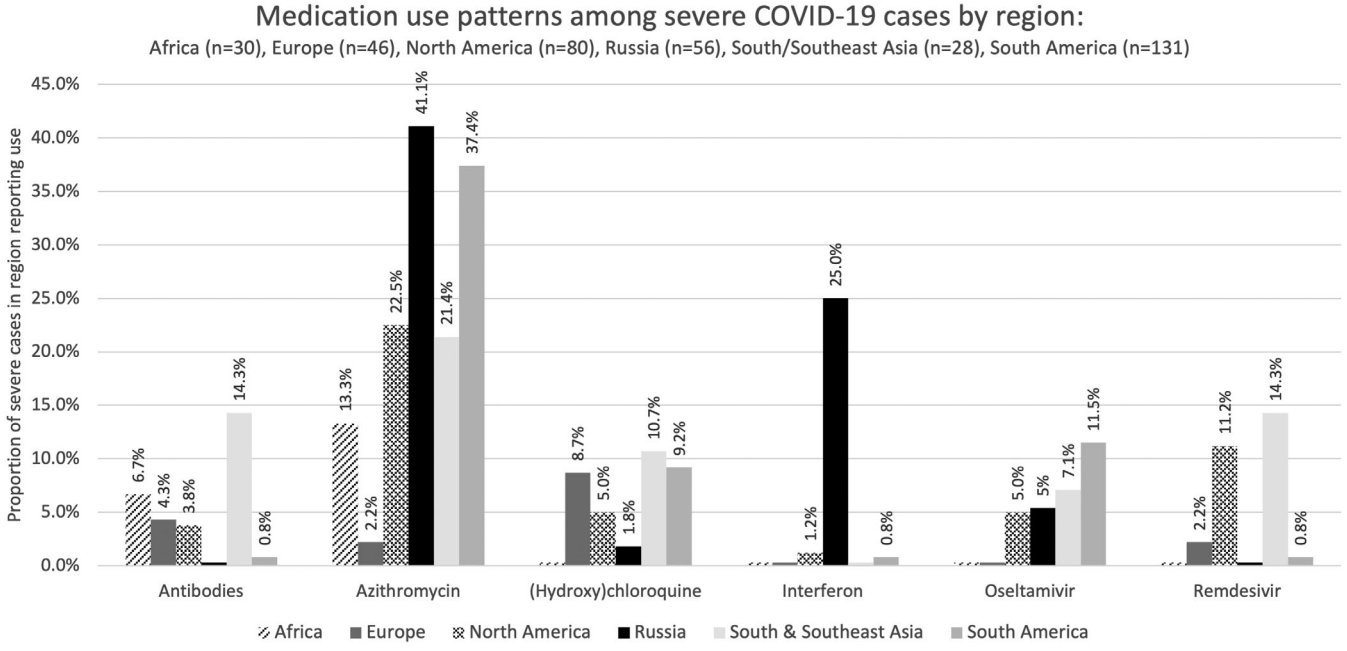

FIGURE 1 COVID-19 medication use patterns among severe COVID-19 cases by region ($n = 371$). Countries by region included: Africa (Ghana, Kenya, Nigeria, and South Africa), Europe (France, Germany, Italy, and Spain), North America (Canada, Mexico, and United States), Russia (Russia), South/Southeast Asia (India, Pakistan, and Philippines), South America (Argentina, Brazil, Chile, Colombia, and Peru)

trimester) demonstrated slightly lower usage during the first trimester, perhaps due to residual confounding by degree of severity within severe COVID-19 cases. However, numbers were small, and estimates are unstable for individual drugs. Among participants with moderate COVID-19 severity, analgesics (43.0% first, 43.6% second, 39.7% third), antibiotics (19.6% first, 20.0% second, 16.5% third), antivirals (3.6% first, 3.6% second, 4.1% third), and biologics (1.2% first, 2.0% second, 1.3% third) all showed similar usage between trimesters.

3.3 | Patterns by country

Differences in drug utilization by country were observed as well. Notably, Russia accounted for the 97.8% of self-reported use of interferon medications (135 out of a total 138 interferon users). Additionally, 52.6% of women who used remdesivir were from the United States, despite the United States only accounting for 12.9% of cases with severe COVID-19 in the study population. India had the highest reported use of antibodies, with 22 (10%) of all participants from India ($n = 221$) reporting receiving antibodies, while only 0.8% of participants overall reported receiving antibody therapy. After restricting to severe COVID-19 cases, reported medication use still varied by location. COVID-19 pharmacotherapy utilization patterns by region among severe cases can be found in Figure 1.

4 | DISCUSSION

In an international cohort of 5780 pregnant women with symptomatic COVID-19 during pregnancy, the most commonly reported COVID-19 treatments other than analgesics were azithromycin, cough suppressants, steroids, interferon, oseltamivir, chloroquine/hydroxychloroquine, antihistamines, and antibodies.

Our findings reveal similar patterns of use found in other, non-pregnant populations with COVID-19, which showed that COVID-19-specific medications were received more frequently among patients with severe disease than in those with lower severity.[13,14] Given the general trend of increased medication use with increased disease severity, future research on the effectiveness and safety of COVID-19 therapeutics in pregnancy will need to carefully adjust for confounding by indication.

The proportion of severe COVID-19 cases was larger in the third trimester. However, within levels of severity, we found similar prevalence of therapy use across trimesters. While these findings are based on small numbers, they highlight the need for further research on COVD-19 drug safety throughout pregnancy, given that medication use is observed in both early and late pregnancy, covering exposure windows susceptible to teratogenic effects.

Some countries accounted for high proportions of utilized drugs, such as Russia's high use of interferon-based drugs and the United States's utilization of remdesivir. In some cases, variable drug approval may explain regional patterns of use, as is the case for Grippferon, an intranasal interferon treatment patented and widely available in Russia. Another explanation for these observed patterns may be resource access, as not all pharmacological treatments are available universally.[15]

Study participants reported taking some medication that is not typically utilized to treat COVID-19, which may also indicate the phenomenon of self-medication to treat symptoms, underscoring the importance of public health messaging to reach vulnerable populations such as pregnant women.

5 | LIMITATIONS

The data were collected via self-reported surveys, resulting in a risk of underreporting and potential misclassification. While study participants were only asked to report medications taken specifically to treat COVID-19, some may have reported all medications they took during their COVID-19 infection. This may explain the reported use of some medications not indicated to treat COVID-19.

Participants could enroll prospectively during pregnancy or within 6 months of end of pregnancy. Temporal proximity to pregnancy and SARS-CoV-2 infection may have influenced respondents' ability to accurately recall medication use. A sensitivity analysis of participants enrolled during pregnancy did not demonstrate substantial differences in reported medication use compared with the entire cohort.

There are also limitations to the disease severity categorization, which does not have the granularity of more complex severity index methods.

6 | CONCLUSION

Participants reported use of treatments for COVID-19 during pregnancy for which there is limited safety information (Table S1). Evaluating the safety of these therapeutics in pregnancy should be a public health priority, since the course of disease in pregnant women with COVID-19 can be severe and treatments may be necessary. Given the lack of pregnant women included in clinical trials, observational studies play an important role in gathering pharmacoepidemiologic evidence to enable informed decision-making in the treatment of pregnant women with COVID-19. Observational studies will need to consider regional differences, trimester of exposure and disease severity.

CONFLICT OF INTEREST

Whitney J. Westhoff and Louisa H. Smith have no conflict to declare. Sonia Hernandez-Diaz reports being an investigator on grants to her institution from Takeda for unrelated studies; and personal fees from UCB and Roche outside the submitted work. She did not receive any funding for this work.

ETHICS STATEMENT

The Institutional Review Board of the Harvard T.H. Chan School of Public Health approved this study (IRB20-0622).

ORCID

Whitney J. Westhoff https://orcid.org/0000-0003-0375-4054

Sonia Hernandez-Diaz https://orcid.org/0000-0003-1458-7642

REFERENCES

1. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *Br Med J*. 2020;370:m3320. doi:10.1136/bmj.m3320
2. Galang RR, Newton SM, Woodworth KR, et al. Risk factors for illness severity among pregnant women with confirmed severe acute respiratory syndrome coronavirus 2 infection—surveillance for emerging threats to mothers and babies network, 22 state, local, and territorial health departments, 29 March 2020–5 March 2021. *Clin Infect Dis*. 2021;73(Supplement_1):S17-S23. doi:10.1093/cid/ciab432
3. Zambrano LD, Ellington S, Strid P, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status — United States, January 22–October 3, 2020. *Morb Mortal Wkly Rep*. 2020;69:1641-1647. doi:10.15585/mmwr.mm6944e3
4. Woodworth KR, Olsen EO'M, Neelam V, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy — SET-NET, 16 jurisdictions, March 29–October 14, 2020. *Morb Mortal Wkly Rep*. 2020;69:1635-1640. doi:10.15585/mmwr.mm6944e2
5. Guo F, Yang X. A comprehensive review of the Management of Pregnant Women with COVID-19: useful information for obstetricians. *Infect Drug Resist*. 2021;14:3363-3378. doi:10.2147/IDR.S325496
6. Sharma D, Sharma N, Sharma P, Subramaniam G. Review of investigational drugs for coronavirus disease 2019. *J Educ Health Promot*. 2021;10:31. doi:10.4103/jehp.jehp_457_20
7. Huybrechts KF, Bateman BT, Zhu Y, et al. Hydroxychloroquine early in pregnancy and risk of birth defects. *Am J Obstet Gynecol*. 2021;224(3):290.e1-290.e22. doi:10.1016/j.ajog.2020.09.007
8. Hernández-Díaz S, Bateman BT, Straub L, et al. Safety of Tenofovir Disoproxil fumarate (TDF) for pregnant women facing the COVID-19 pandemic. *Am J Epidemiol*. 2021;190:2339-2349. doi:10.1093/aje/kwab109
9. D'Souza R, Ashraf R, Rowe H, et al. Pregnancy and COVID-19: pharmacologic considerations. *Ultrasound Obstet Gynecol*. 2021;57(2):195-203. doi:10.1002/uog.23116
10. Jorgensen SCJ, Lapinsky SE. Tocilizumab for coronavirus disease 2019 in pregnancy and lactation: a narrative review. *Clin Microbiol Infect*. 2022;28:51-57. doi:10.1016/j.cmi.2021.08.016
11. Jorgensen SCJ, Davis MR, Lapinsky SE. A review of remdesivir for COVID-19 in pregnancy and lactation. *J Antimicrob Chemother*. 2021:dkab311. doi:10.1093/jac/dkab311, 77, 24, 30
12. Hernández-Díaz S, Smith LH, Dollinger C, Rasmussen SA, Schisterman EF, Bellocco R, Wyszynski DF. International registry of coronavirus exposure in pregnancy (IRCEP) — cohort description and methodological considerations. *Am J Epidemiol*. 2022;kwac046. doi:10.1093/aje/kwac046
13. Lin KJ, Schneeweiss S, Tesfaye H, et al. Pharmacotherapy for hospitalized patients with COVID-19: treatment patterns by disease severity. *Drugs*. 2020;80:1961-1972. doi:10.1007/s40265-020-01424-7
14. Cocoros NM, Fuller CC, Adimadhyam S, et al. A COVID-19-ready public health surveillance system: the Food and Drug Administration's sentinel system. *Pharmacoepidemiol Drug Saf*. 2021;30(7):827-837. doi:10.1002/pds.5240
15. Hospitals Are Rationing Remdesivir - WSJ.2021 Accessed November 17, 2021. https://www.wsj.com/articles/location-plays-big-role-in-patient-access-to-first-covid-19-drug-11590157424

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Westhoff WJ, Smith LH, Wyszynski DF, Hernandez-Diaz S. COVID-19 pharmacotherapy utilization patterns during pregnancy: International Registry of Coronavirus Exposure in Pregnancy. *Pharmacoepidemiol Drug Saf*. 2022;1-6. doi:10.1002/pds.5440