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

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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.preregistry.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
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.

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

| Drug                          | Mild   | Moderate | Severe | Overall  |
|------------------------------|--------|----------|--------|----------|
|                              | (n = 2355) | (n = 3053) | (n = 372) | (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.
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 pharmaceutical 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/m². 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 trimester, 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 trimester) were used more frequently in later gestations. The frequency of use of anticoagulants (9.1% first trimester, 15.3% second trimester, 17.4% third trimester) and steroids (15.3% first trimester, 12.7% second trimester, 10.7% third trimester) also increased with gestational age.

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)
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 medication (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.

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.
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SUPPORTING INFORMATION

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

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