Antiviral Treatment on Pregnancy with COVID-19 Infection : A Systematic Review

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Abstract
Objective to evaluate antiviral treatment, duration, and side effects on pregnant women based on gestational age and severity of COVID-19 infection. Method**:** a systematic review of antiviral treatment, duration, and side effects on pregnant women based on gestational age and severity of COVID-19 infection. Systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement. Result 948 papers accessed through Pubmed, Scopus, Science Direct, Cohcrane, and other with keywords "Antiviral", "Pregnancy" "Pregnant" "Coronavirus" "COVID-19" "SARS-CoV-2". Duplicate papers were excluded (n=302), topics and abstracts that do not meet the criteria (n=612), and 25 papers that did not meet the inclusion criteria. 9 papers that meet the inclusion criteria (case reports and cohort retrospective case study) discussed 20 pregnant women with COVID-19 infection (16 moderate and severe cases received Remdesivir, 3 moderate and mild cases received Lopinavir-ritonavir combination, and 1 moderate case received Arbidol). Conclusion, remdesivir is an antiviral frequently used in pregnancy on trimester II and III with severe COVID-19 infection with a duration of treatment of 5-10 days. Remdesivir should be monitored because some show side effects of increasing liver function.

Key word: *Antiviral, Pregnant, COVID-19*

Pengobatan Ibu Hamil yang Terinfeksi COVID−19 dengan Antivirus

Abstrak
Tujuan untuk mengevaluasi penggunaan obat antivirus, lama pengobatan, dan efek samping pada wanita hamil dengan infeksi COVID-19 berdasarkan usia kehamilan dan derajat keparahan. Metode tinjauan literatur sistematis tentang penggunaan obat antivirus, lama pengobatan, dan efek samping pada wanita hamil dengan infeksi COVID-19 berdasarkan usia kehamilan dan tingkat keparahan. Tinjauan sistematis mengikuti pedoman dari *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA). Hasil terdapat 948 jurnal yang diakses melalui Pubmed, Scopus, Science Direct, Cohcrane dan lainya dengan kata kunci : Antiviral, Pregnancy, Pregnant, Coronavirus, COVID-19, SARS-CoV-2. Terdapat jurnal yang terduplikasi (n=302), topik dan abstrak yang tidak sesuai kriteria (n=612), dan 25 jurnal yang tidak sesuai kriteria inklusi. Terdapat 9 jurnal yang memenuhi kriteria inklusi (laporan kasus dan studi retrosepktif kohort) yang membahas 20 wanita hamil dengan infeksi COVID-19 (16 kasus dengan derajat sedang dan berat menerima Remdesivir, 3 kasus derajat sedang dan ringan menerima kombinasi Lopinavir-ritonavir, dan 1 kasus derajat sedang menerima Arbidol). Kesimpulan, remdesivir adalah antivirus yang sering digunakan pada wanita hamil trisemester II dan III dengan infeksi COVID-19 derajat berat, lama pengobatan 5-10 hari. Remdesivir harus diwaspadai karena dapat menimbulkan efek samping seperti peningkatan fungsi hati.

Kata kunci: Antivirus, Hamil, COVID-19

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China, is now a global outbreak of disease.[1,2]

Treatments are rapidly evolving during the time of this deadly pandemic and several drugs remain under investigation as potential therapies for critically ill COVID-19 patients.[3] Proposed potential antiviral effect treatment options include, drugs such as chloroquine, metformin, remdesivir, and lopinavir/ritonavir for pregnant women with SARS CoV-2 are worth considering. Other potential therapies which are contraindicated in pregnancy include ribavirin because ribavirin has teratogenic properties; It induces miscarriages and leads to craniofacial and limb defects in mouse models.[4,5] Until now, there is no drug of choice in pregnancy with COVID-19 infection, therefore the authors would like to reviewing papers (case reports and cohort retrospective case study) according to a systematic review about the of the antiviral treatment, duration, and side effects on pregnant women based on gestational age and severity of COVID-19 infection.

Method

Search strategy

Four electronic search engines (i.e., PubMed, Scopus, Science Direct, and Cohcrane) and other were chosen to detect the manuscripts on the topic "Antiviral, COVID-19 and pregnancy". The selection of the scientific evidence was based on the identification of antiviral, COVID-19, and pregnancy. The search included papers published from December 2019 to August 2021. The search was restricted to papers with unavailable full-text, and irrelevant topics and manuscripts written in English language also omitted. Several keywords, combined in different strings depending on the electronic database, were chosen: "Antiviral", "Pregnant", "Pregnancy", "Coronavirus", "COVID-19", "SARS-CoV-2". To improve the diagnostic accuracy of the search, we also performed a manual search of the list of references.

Study selection

Manuscripts describing the antiviral and its dose, duration of antiviral treatment, and side effects associated with a pregnancy and a concomitant COVID-19 were considered suitable for the present analysis. All the studies with an observational design were selected: case-report, case-series, cross-sectional, case-control, and cohort (both prospective and retrospective) studies data on pregnant women with COVID-19 infection. The following exclusion criteria were adopted: 1) Editorials, reviews, correspondences, clinical opinion; 2) Dissertations; 3) Management guidelines; 4) Studies performed in vitro; 3) Studies which recruited animals.

Papers are identified using the keywords described above. After removing duplicates using Microsoft Excel program, retrieved papers are screened based on their titles and abstracts to evaluate the suitability of the manuscript based on the above-mentioned inclusion and exclusion criteria. The first assessment, carried out by two investigators (APK and GIK), was supervised by a third investigator (TPS). The assessment of the selected full texts, as well as the extraction of the outcome and independent variables, was performed by the same investigators.

Data extraction

An ad hoc electronic form (excel file) was prepared to collect qualitative variables. Two investigators (APK dan GIK) independently retrieved data from the results sections of the selected papers. In the majority of the cases data were aggregated. On this basis, a local ethical approval was not needed. The following study, antiviral, pregnant, and covid-related variables were collected: 1)

First author; 2) Publication date; 3) Number of cases; 4) The age of the mother; 5) Gestational age; 6) Severity of COVID-19; 7) Type of Antiviral; 8) Dose; 9) Duration of treatment; 10) Side effect.

Study quality assessment

The systematic review was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [6].

Case-report and case-series were evaluated following the quality scale "Methodological quality and synthesis of case-series and case-reports". [7]

Result

Of the 948 papers initially identified, 302 were duplicates and excluded (Fig. 1). 646 papers were screened by two reviewers for reporting of COVID-19 infection during pregnancy. Discordant review determinations were reconciled by discussion between reviewers. Papers were excluded based on title and abstract review for the following mutually exclusive reasons: did not report data related to COVID-19 infection in humans (n=317); did not report data among pregnant (n=130); did not report on any antiviral treatment (n = 120); review article, clinical opinions, or management guideline (n=39); full English text not available (n=6).

We completed full-text reviews on 34 papers to identify studies with case-level data. Twenty-five papers were further excluded (14 papers were literature review, 3 papers do not contain pregnant woman population, 3 papers were non-free access journals, 3 papers do not reported specific antiviral not reported, and 2 papers were clinical opinion). 9 final papers (8 case reports and 1 cohort retrospective case study) that meet the inclusion criteria are arranged for systematic

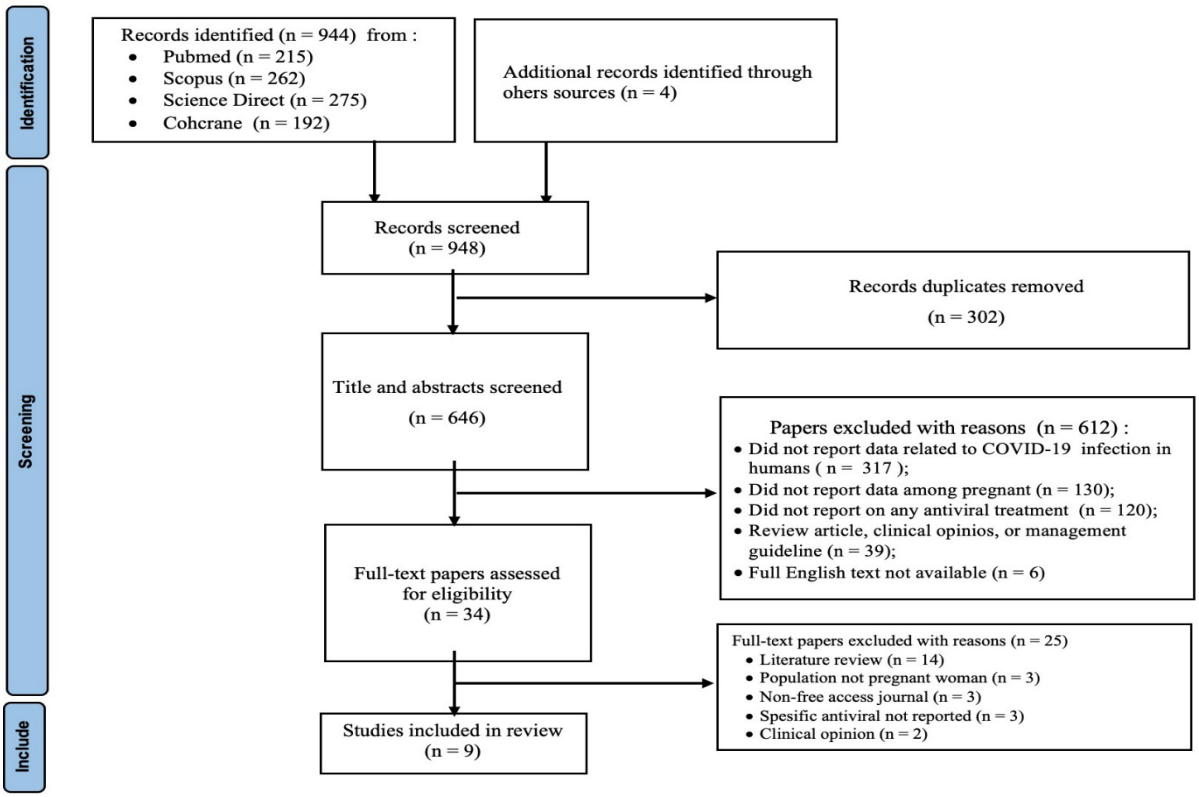

Figure 1 Flowchart Summarizing Literature Search and Selection Process for Review of Antiviral Therapy for Pregnant Women with COVID-19 Infection

review.

Among 20 pregnant women with COVID-19 infection, ages ranged from 25 to 42 years (median 34, interquartile range 27–33). Gestational age at time of symptom onset or diagnosis among pregnant women ranged from 16 to 40 completed weeks (median 30.9, interquartile range 25–31); Seven women presented in the second trimester, and thirteen presented in the third trimester (Table 1). Other than severity that mentioned in the reports, for incomplete reports, we also conclude the severity level based on the clinical symptoms report.[8] The severity of COVID-19 infections was reported for seventeen patients: Severe illness (n = 15), moderate illness (n = 4), and mild illness (n = 1).

Among 20 case reports describing antiviral treatment, sixteen pregnant women received the antiviral remdesivir.[9-17] The dose of remdesivir given was a regimen of 200 mg intravenous (IV) on day 1 followed by 100 mg IV daily. Duration of administration of remdesivir varies, from 2 until 10 days, this difference in the duration of administration depends on the improvement in clinical symptoms and side effects such as increase of aspartate transaminase levels, transaminitis, and hepatitis that occur when given remdesivir.[10,11]

Three pregnant women received antiviral combination Lopinavir-ritonavir.[16-17] The dose of combination antiviral given are two women receiving 200/50 mg two tablets twice a day and the other receiving 400/100 mg administered orally every 8 hours with duration of administration are eight and ten days. No side effects were reported from the mother and the neonatus.

One pregnant woman also received Arbidol also known as Umifenovir with dose 0.2g administered orally every 8 hours, with unspecified duration of administration.[16]

Table 1 Published studies of Antiviral in the Treatment of COVID−19 in Pregnancy from Case Report and Cohort Retrospective Case Study

Authors	Publication date	Number of Cases	The Age of the mother *	Gestational Age**	Severity of COVID-19	Type of Antiviral	Dose	Duration Of Treatment	Side Effect
Naqvi, Mariam, et all	Nov 2020	1	35	22,2	Severe	Remdesivir	Day 1 : 200 mg Day 2-5: 100 mg	5 Days	None
Jennifer A. Mccoy,et all	Jun 2021	5	1) 27 2) 39 3) 33 4) 29 5) 41	1) 16 2) 28 3) 26 4) 31 5) 31	1) Severe 2) Severe 3) Severe 4) Severe 5) Severe	Remdesivir	200 mg IV on day 1 followed by 100 mg IV	1) 4 Days 2) 6 Days 3) 9 Days 4) 10 Days 5) 4 Days	1) None 2) Worsening AST 3) AST mild increase 4) None 5) None
Irogue Igbinosa, et all	Agt 2020	3	1) 25 2) 28 3) 29	1) 34 2) 25 3) 25	1) Severe 2) Severe 3) Severe	Remdesivir	1) 3 Dose 2) 8 Dose 3) 2 Dose	1) 3 Days 2) 8 Days 3) 2 Days	1) Hepatitis, Transaminitis 2) None 3) None
Ranadheer Dande, et all	Jan 2021	1	39	29	Moderate	Remdesivir	Day 1 : 200 mg Day 2-5 : 100 mg	5 Days	None
Yudianto Budi Saroyo, et all	May 2021	5	1) 27 2) 28 3) 31 4) 30 5) 35	1) 27,4 2) 36 3) 40 4) 32 5) 27	1) Severe 2) Severe 3) Severe 4) Severe 5) Moderate	Remdesivir	Day 1: 200 mg IV/daily Day 2–5: 100 mg IV/daily	1) 5 Days 2) 5 Days 3) 5 Days 4) 5 Days 5) 5 Days	1) None 2) None 3) None 4) None 5) None
Grace A. Maldarelli, et all	Agt 2020	1	39	34,4	Severe	Remdesivir	NR	8 Days	None
Jennifer Jacobson, et all	Nov 2020	1	42	26	Severe	Remdesivir	Day 1: 200 mg IV/daily Day 2–10: 100 mg IV/daily	10 Days	None
Ifeoma Ogamba , et all	Apr 2021	2	1) 29 2) 33	1) 34,7 2) 34,5	1) Moderate 2) Mild	1) Lopinavir-ritonavir 2) Lopinavir-ritonavir	1) 200/50 mg 2 tab 2x1 2) 200/50 mg 2 tab 2x1	1) 10 Days 2) 8 Days	1) None 2) None
Xiaotong Wang, et all	Feb 2021	1	28	30	Moderate	1) Arbidol 2) Lopinavir-Ritonavir	1) 0.2g PO/ 8 hours 2) 400/100 mg PO/ 8 hours	NR	None

*In years. **In weeks. AST: Aspartate Transaminase; NR: Not Reported.

There are no side effects that occur when Arbidol is given.

Discussion

Pregnant woman are susceptible to respiratory pathogens and severe pneumonia because of the change during pregnancy (i.e increased oxygen consumption, elevated diaphragm, and edema of the respiratory tract mucosa) that cause pregnant women become intolerance to hypoxia.[18] The Society of Maternal-Fetal Medicine (SMFM) recently defined the severity scale of COVID-19 infection which includes asymptomatic, mild, moderate, severe, and critical disease.[8] We can see from 15 pregnant women, all of them have severe illness, which all the women have hypoxia with oxygen saturation less than or equal to 93%, and some even experienced Acute Respiratory Distress Syndrome (ARDS).

Moderate and severe clinical symptoms of COVID-19 in this study received antiviral treatment remdesivir. Remdesivir or Veklury, is an amino phosphoramidate prodrug and metabolized into its active form, which can obscure viral RNA polymerase and evade proofreading by viral exonuclease, thereby causing a decrease in viral RNA production.[19] Remdesivir suggest safety for pregnancy this data acquired from a randomized controlled trial (RCT) during the Ebola epidemic.[20] The suggested clinical regimen for treatment of patients with COVID-19 is a loading dose of Remdesivir 200 mg IV, followed by daily doses of 100 mg IV for up to 10 days.[21] Only emergency Use (EUA) of Remdesivir has been approved by FDA as an antiviral to treat COVID-19 in adults and pediatric patients 12 years of age and older and weighing at least 40 kg requiring hospitalization.[22] A new study demonstrated the remdesivir treatment have clinical improvement on 68% severe COVID-19 patients.[23] A recent double-blind, randomized, placebo controlled trial of intravenous remdesivir in adults hospitalized with COVID-19 showed that Remdesivir have shorter recovering time then the placebo.[24] Remdesivir is not recommended to given in patients with liver function tests (LFTs) exceeding five times the upper limit of normal (ULN), because this antiviral has been associated with elevation of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST).[25]

Lopinavir–ritonavir was chosen to treat moderate and mild symptoms of the COVID-19 infection.[15-16] RCT have done, with the dose were 400 mg and 100 mg by mouth a day for 10-14 days, but for COVID-19 therapy still unclear.[26,27] Recent recommendation report Lopinavir-ritonavir were used to avoid use because the efficacy is unclear at this time, unless used in a clinical trial and also due to adverse effects of arrhythmia. Limited data has shown that lopinavir-ritonavir inhibits SARS-CoV-2 in vitro.[28] US Food and Drug Administration (FDA) put Lopinavir–ritonavir in pregnancy as category C medication used for the treatment of HIV. Category C means that animal reproductive studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans; therefore, whether treatment with category C medication will harm a baby is unknown.[29] Furthermore, Lopinavir–ritonavir administration in rate of preterm deliveries, low-birth-weight neonates, stillbirths, and birth defects did not increase.[30] But we can see here, Lopinavir–ritonavir was chosen to treat moderate and mild symptoms of the COVID-19 infection with no side effects.[15,16]

One case in treating moderate symptoms of COVID-19 using arbidol.[16] Russian antiviral drug, as known as Arbidol is a that seems to be effective against viruses like influenza A, B, and C, respiratory syncytial virus (RSV), and severe acute respiratory syndrome-related coronavirus (SARS-CoV),[31] National Health Commission of the China recommend Arbidol for treatment of

COVID-19.[32] Dose of Arbidol for COVID-19 therapy from Randomised controlled trial that have done, were 200 mg three times daily, 7 to 14 days based on the severity of disease. However, it should be noted that this RCT did not include pregnant women as inclusion criteria.[31] Arbidol also revealed by a retrospective study including 69 adults beside pregnant women, showed a tendency to the discharging rate and decrease mortality. [1] In study by Wang et al, it report that pregnant women with COVID-19 who were given arbidol recovered without any side effects, although reporting on the duration of treatment was incomplete.[16]

Conclusion

In this systematic review, Remdesivir is the most common antiviral used on pregnancy with COVID-19 with an early dose on the first day 200 mg and 100 mg for the next day for 5-10 day. Remdesivir administration can be used on moderate and severe illness of COVID-19 in second and third trimesters of pregnancy. Administration of this antiviral should be monitored for showing some side effects in elevating liver function (LFT). The provision of Lopinavir–ritonavir, given dose 400 mg and 100 mg by mouth a day for 10-14 days, is also quite often used for mild and moderate COVID-19 infection in third trimesters and there have been yet side effects recorded. Arbidol is less often used for pregnancy with COVID-19 infection, with dose 200 mg three times daily for 7 to 14 days, it has been shown to provide recovery with combination Lopinavir–ritonavir for COVID-19 infection in the third trimester.

Limitations

This author realizes that this paper is not perfect because some papers are not accessed due to language limitations and not free-access paper.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this systematic review.

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