JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12911

The use of Remdesivir in pregnant women with COVID-19

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Received: 2022-11-04.
Accepted: 2022-12-25

J Clin Med Kaz 2023; 20(1):31-34

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Abstract

Objectives: This study was conducted to investigate the use of Remdesivir among pregnant women with probable and confirmed Covid-19 coronavirus infection.

Material and methods: To implement the study, a comprehensive examination of 120 pregnant women with severe and extremely severe forms of coronavirus infection was conducted.

Results: Statistically significant differences were obtained (p=0.019) at the time of comparison between the main and control groups, depending on the age of the subjects. The studied differences are due to the higher frequency of the age group 33-42 years among patients taking Remdesivir compared to those who were in the control group (p = 0.036). Women of the main group (Me = 9.00; Q1-Q3 = 8.00-11.0) stayed longer in the hospital compared to women in the control group (Me = 8.00; Q1-Q3 = 7.00-10.0). The more severe condition of patients in this group is cause of that. There are statistically significant differences in changes in amniotic fluid according to ultrasound data in the control and main groups (p=0.013). According to the results of our study, it was found that the decrease in temperature to a normal level occurred earlier in the control group (68%) than in the main group.

Conclusion: The older age group and the third trimester of pregnancy are risk factors for the transition to a severe form of the disease. Reliable efficacy of the etiotropic drug Remdesivir could not be traced.

Key words: COVID-19, pregnancy, Remdesivir

Introduction

The Covid-19 coronavirus infection is a disease characterized by relentless progression and an increase in infections and deaths since when it is discovered in China in December 2019. Currently, SARS-CoV-2 is continuously transforming into new mutations as it replicates: B .1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), B.1.617. 2 (Delta), and the latest version B.1.1.529 (Omicron) released at the end of 2021. The most modified version of Omicron has about fifty mutations, 32 of which are in the spike protein [1]. As of October 17, 2022, the total number of cases in the world was 629,959,595, of which 6,571,489 deaths. In our republic, the total number of cases was 139,287, of which 13,692 were deaths. At the same time, 959 people continue to receive treatment, of which 107 patients are in hospitals, and 852 patients are on an outpatient basis. 3 patients are in serious condition, 3 patients are in a state of extreme severity, 1 patient is on mechanical ventilation [2, 3]. It should be noted that, 38 thousand 149 cases were registered in our city, of which 1646 were pregnant for the period 2020-2022: 537 - in 2020, 892 - in 2021, 217 - women in 2022 [3]. The most vulnerable group of people to COVID-19 includes not only the elderly, but also pregnant women. At the beginning of the COVID-19 pandemic, studies conducted by American and Chinese scientists revealed that the risk of transition to a severe course of the disease in pregnant women was higher than in non-pregnant ones [1, 4-6]. The progression of the disease caused by the SARS-CoV-2 virus is directly dependent on the entry of the virus into host cells after binding to angiotensin-converting enzyme 2 (ACE2). ACE2 replicates on cell membranes and tropen in the placenta throughout pregnancy. This phenomenon is a possible etiology of

predisposition of pregnant women to COVID-19 [1]. Reduced immune reactivity and other physiological changes during gestation cause an increased susceptibility to respiratory diseases and severe pneumonia in pregnant women, which can lead to hospitalization in intensive care units and mechanical ventilation [7]. A lightning-fast development of a critical condition is possible against the background of a fairly stable course of the disease in pregnant women with coronavirus infection COVID-19 [8]. A systematic review including 18 studies found that the most common symptoms in pregnant women were fever (87.5%) and cough (53.8%). In addition, fatigue (22.5%), diarrhea (8.8%), shortness of breath (11.3%), sore throat (7.5%) and myalgia (16.3%) are common [9]. The treatment of COVID-19 is significantly complicated by the lack of a single generally accepted protocol for the treatment of various clinical forms of this disease. This issue is especially relevant in relation to pregnant women, as drugs have a possible effect on the fetus. The coronavirus pandemic has led to the need to prescribe drugs to pregnant women with no evidence of effectiveness and no guarantee of serious consequences for the fetus. The main dilemma for scientists was the creation of a drug that suppresses SARS-CoV-2. The antiviral drug Remdesivir, due to a positive past, was urgently used for pregnant women with COVID-19. [10]. In Kazakhstan, from August 5, 2021, women during the gestation period are prescribed Remdesivir intravenously as an etiotropic drug according to the scheme intravenously of 200 mg on the 1st day, then 100 mg daily, course of 5 days [10]. This drug is included in the prescription list for patients based on foreign and domestic experience [10-12]. Our aim was to study the effectiveness of the use of Remdesivir in pregnant women with coronavirus infection Covid-19.

Material and methods

This study is a retrospective, cohort, analytical, non-interventional study. We analyzed 120 cases of pregnant women admitted to the city infectious diseases center from December 2021 to May 2022 with severe and extremely severe forms of COVID-19 coronavirus infection. The subject of the study were pregnant women with severe and extremely severe forms of coronavirus infection COVID-19. Inclusion criteria: confirmed and probable cases of coronavirus infection in pregnant women, use of Remdesivir, severe and extremely severe Covid-19. Criteria for exclusion from the study: pregnancy without Covid-19, mild and moderate severity of the disease in pregnant women.

Statistical analysis

The normality of the distribution was checked according to Kolmogorov-Smirnov with the Lilliefors correction. Since all data showed a non-normal distribution, the median and interquartile range were subsequently used. Categorical variables are presented as absolute numbers, percentages, and frequencies. A $p<0.05$ value was considered statistically significant. Statistical processing of the obtained data was carried out using the IBM SPSS Statistics 26.0 program. Nominal variables were analyzed using Pearson's chi-square test, Fisher's exact test, odds ratio, and relative risk.

Ethics

The study was approved by the Local Bioethical Committee of JSC "SKMA" (date: 03/16/2021). Written informed consent for publication in the article was obtained from patients or their legal representatives.

Results

Patients were divided into two groups, depending on the use of the antiviral drug remdesivir, 60 pregnant women each. The highest incidence rate by trimester was obtained in both groups in the period from 28 to 40 weeks (63.3% and 65%, respectively) (Figure 1).

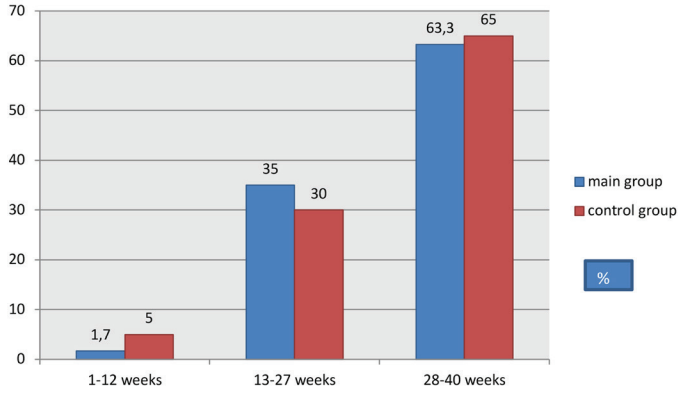

Figure 1 - Distribution of women depending on the duration of pregnancy

During the study, it was found that women in the age group from 33 to 42 years in the main group met more often than in the comparison group ($p = 0.019$). According to Cramer's V, a correlation of medium closeness was observed ($V = 0.250$). The antiviral drug Remdesivir was prescribed to women who had 5 or more pregnancies (25.0%), and in the presence of 4 or more pregnancies - 18.3%. In the analysis of pregnant women, depending on the diagnosis, according to the PCR result, statistically significant differences were obtained ($p = 0.02$).

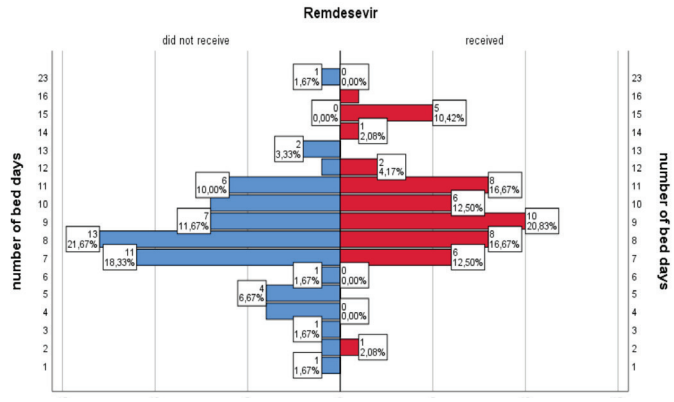

Figure 2 - Number of hospital bed days for pregnant women with coronavirus infection COVID - 19

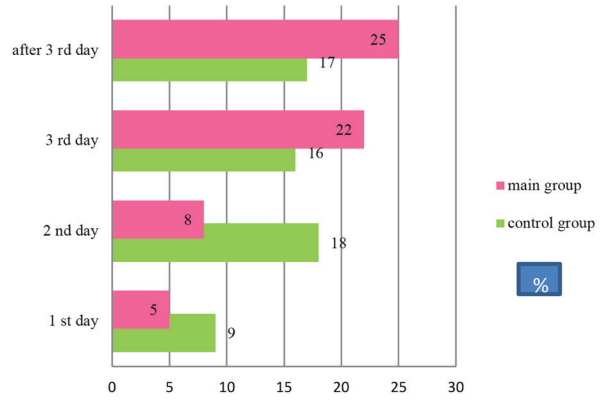

Figure 3 - Dynamics of improvement in the RR indicator

Table 1 Comparative table of age, gestation parity among pregnant women with COVID-19, confirmed and probable cases

Index		Therapy with Remdesivir (n=60)		Therapy without Remdesivir (n=60)		p
		Abs.	%	Abs.	%	
Age, full years	18-25	17	28,3	22	36,7	0,019*
	26-32	18	30,0	27	45,0	
	33-42	25	41,7	11	18,3	
Pregnancy parity	1	6	10,0	17	28,3	0,111
	2	14	23,3	8	13,3	
	3	14	23,3	12	20,0	
	4	11	18,3	8	13,3	
	5 и more	15	25,0	15	25,0	
Diagnosis based on the PCR result	U07.1	48	80	54	90	0,02*
	U07.2	12	20	6	10	

* - differences in indicators are statistically significant (p<0,05)

One of the indicators by which women in the gestation period were studied was the number of bed-days spent in the hospital, shown in Figure 2.

When comparing the main and control groups in terms of the number of bed-days, statistically significant differences were established (p=0.001). Women in the main group (Me = 9.00; Q1-Q3 = 8.00-11.0) stayed longer in the hospital compared to those who were in the control group (Me = 8.00; Q1-Q3 = 7.00-10, 0). This is caused by the more severe condition of patients in this group.

We took the following criteria for the effectiveness of Remdesivir therapy among pregnant women with COVID-19: the timing of temperature normalization, an improvement in respiratory rate, and a subjective decrease in dyspnea. In the Remdesivir group, the subjective sensation of shortness of breath ended on day 2 in 4 pregnant women (6.6%), on day 3 in 11 pregnant women (18.3%), after day 3 in 40 patients (66.6%) (Figure 3).

A decrease in body temperature to normal values in the group without Remdesivir therapy on days 1-2 was observed in 68% (41) of pregnant women, which is associated with a less severe course of COVID-19 in this group of patients, while in the main group - in 28% (17) research. An increase in SpO_2 by more than 95% and the abolition of oxygen therapy on the 1st-2nd day in the main group in 71% (43), up to 4 days from the start of antiviral therapy in 10% (6) of cases, but only in 68% (41) cases on the 7-8th day after the start of etiotropic treatment. In another group, more than 95% withdrawal of oxygen therapy was observed in 26 pregnant women (43%) on the 1st day, in 38% (23) on the 3rd-4th day, in 15% 9) - on the 5th-6th day; 4% (2) - after 7-8 days from the start of therapy.

Discussion

Coronavirus infection COVID-19 is an ongoing dilemma around the world. Scientists are constantly striving to come to a consensus regarding the treatment of patients. However, the constant transformation of the virus does not solve this issue. The status of treatment of pregnant women with COVID-19 is higher, which is associated with the risk of possible teratogenic effects of drugs [13,14]. The COVID-19 pandemic has led to the prescription of a huge number of drugs without an evidence base and no guarantee of long-term effects on the fetus [13]. The development of drugs for etiotropic treatment takes a long process, so the effectiveness of existing antiviral drugs was studied. One of these was Remdesivir, which previously showed good results, and was eventually urgently prescribed to pregnant women with COVID-19 [13-16]. To evaluate the efficacy and safety of the antiviral drug Remdesivir in pregnant women with COVID-19, further studies are needed to be included in international recommendations for the treatment of coronavirus infection COVID-19 [13-16].

During the study, it was found that in the main group, the age group from 33 to 42 years old made up the majority (41.7%). The course of coronavirus infection is aggravated in multiparous women and in the third trimester of pregnancy. Women who received antiviral therapy stayed in the hospital for 2 bed-days longer than pregnant women in the control group. The criteria for the effectiveness of Remdesivir in women in the gestational period with COVID-19 were the dynamics of temperature normalization, improvement in respiratory rate, and subjective reduction in dyspnea. According to the results of our study, it was found that the decrease in temperature to a normal level occurred earlier in the control group (68%) than in the main group. Subsequently, an increase in SpO_2 by more than 95% in more patients was observed on days 3-4 in the main group (71%) and on days 1-2 in the control group (43%). After 3 days in the main group, respiratory rate improved (41.6%) and a decrease in subjective dyspnea (66.6%).

A randomized controlled trial (RCT) showed that Remdesivir therapy in pregnant women with Ebola was safe and without significant side effects [17]. The use of this antiviral drug for moderate to severe COVID-19 requiring oxygenation has shown modest benefit [18]. This was also confirmed in our study. According to various authors, among pregnant women with SARS-CoV-2 coronavirus infection, the use of Remdesivir for 5 days leads to a clinical improvement in the course of moderate COVID-19 [19], which is consistent with data in the general population [20]. Berwick et al. reported that Remdesivir given intravenously for 10 days clinically improves severe COVID-19 in pregnant and postpartum patients [21]. But in our study, the use of a 5-day course of Remdesivir showed no clinical improvement in patients.

Recruitment of pregnant women with COVID-19 during the pandemic has been rapid, which is one of the strengths of the study. However, the limitation was the creation of a comparison group. The prescription list for patients with severe and extremely severe COVID-19 included the antiviral drug Remdesivir. Therefore, the comparison group included those pregnant women who did not give informed consent to additional treatment. Another limitation was that this study is single center, which does not provide extended results. It should be noted that the sample size was relatively small.

Conclusion

The use of Remdesivir in the appointment of pregnant women for the treatment of COVID-19 has not shown positive results. However, the application must be carefully monitored to detect adverse reactions. Also, as a result of the study, it was found that multiparous women are prone to a more severe course of coronavirus infection. The older age group and the third trimester of pregnancy are risk factors for the transition to a severe form of the disease. Further studies are needed to evaluate the efficacy and safety of the antiviral drug Remdesivir in pregnant women with COVID-19 for inclusion in international recommendations for the treatment of coronavirus infection COVID-19

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

References

1. Kumar D, Verma S, Mysorekar IU. COVID-19 and pregnancy: clinical outcomes; mechanisms, and vaccine efficacy. *Transl Res*. 2022; 12:S1931-5244(22)00180-3. https://doi.org/10.1016/j.trsl.2022.08.007
2. https://ourworldindata.org/explorers/coronavirus-data-explorer 07/16/2022
3. Data of the committee for sanitary and epidemiological control of the city of Shymkent, 2022. https://rk-ncph.kz/ru/sanepidem/ezhemesyachnaya-situatsiya
4. Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, Sabbour M, Gebril S, Nasser M, Kamel M, Amir A. A systematic scoping review of COVID-19 during pregnancy and childbirth. *International Journal of Gynecology & Obstetrics.* 2020;150(1):47-52. https://doi.org/10.1002/ijgo.13182
5. Fan C, Lei D, Fang C, Li C, Wang M, Liu Y, Bao Y, Sun Y, Huang J, Guo Y, Yu Y. Perinatal transmission of 2019 coronavirus Disease–Associated severe acute respiratory syndrome coronavirus 2: should we worry? *Clinical Infectious Diseases.* 2021;72(5):862-4. https://doi.org/10.1093/cid/ciaa226
6. Yan J, Guo J, Fan C, Juan J, Yu X, Li J, Feng L, Li C, Chen H, Qiao Y, Lei D. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. *American journal of obstetrics and gynecology.* 2020;223(1):111-e1. https://doi.org/10.1016/j.ajog.2020.04.014
7. Alfaraj S. H., Al-Tawfiq J. A., Memish Z. A. Middle East respiratory syndrome coronavirus (MERS-CoV) infection during pregnancy: reportof two cases and review of the literature. J. Microbiol. Immunol. *Infect*. 2019; 52(3):501—503. ttps://doi.org/10.1016/j.jmii.2018.04.005
8. Hong L,Smith N.,Keerthy M., Lee-Griffith M.,Garsia R et al. Severe COVID-19 infection in Pregnancy Recuiring Intubation without Preterm Delivery: A Case Report . *Case Reports in Womens Health.* 2020; 27. https://doi.org/10.1016/j.crwh.2020.e00217
9. Liu D et al. Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis. *AJR Am J Roentgenol.* 2020; 18:1-6. https://doi.org/10.2214/AJR.20.23072
10. Clinical protocol for the diagnosis and treatment of coronavirus infection COVID-19 in pregnant women, women in labor and puerperas of August 5, 2021. http://www.rcrz.kz/index.php/ru/2017-03-12-10-50-44/press-reliz/2365-press-reliz- 16.07.2022
11. Giniyat A.G., Kulzhanova Sh. A., Tuleshova G.T., Konkayeva M.E., Smagulova Z. K., Beisenbieva N.Ye., Utegenova A.M., Turebaeva G.O., Nurakhmetova G.A., Bolatov A. Clinical efficacy of the antiviral drug remdesivir in the comprehensive treatment of patients with COVID-19. *Nauka i Zdravookhranenie [Science & Healthcare]*. 2021; 3(23):6-15. https://doi.org/10.34689/SH.2021.23.3.001
12. Shaimerdenova G.G., Abuova G.N. Evaluation of the effectiveness of Remdesivir in pregnant women with Covid-19. Pharmacy. 2022; 5(244):47-53. https://doi.org/10.53511/pharmkaz.2022.79.74.006
13. Vitiello A, Ferrara F, Zovi A, Trama U, Boccellino M. Pregnancy and COVID-19, focus on vaccine and pharmacological treatment. J Reprod Immunol. 2022; 151:103630. https://doi.org/10.1016/j.jri.2022.103630
14. H. Chen, J. Guo, C. Wang, F. Luo, X. Yu, W. Zhang, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020; 395 (10226):809-815. https://doi.org/10.1016/S0140-6736(20)30360-3
15. Shaimerdenova G.G., Abuova G.N., ZhumabekovaS.Zh., KaldybekovaZh.S. Clinic of COVID-19 in pregnant women. Principles of treatment in infectious disease hospitals of Shymkent. Aktualnyeproblemyteoreteticheskoyiklinicheskoymediciny. 2021; 1:59-62.
16. Goldman J.D., Lye D.CB., Hui D.S., Marks K.M., Bruno R. and Montejano R. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med.* 2020; 383(19):1827-37. https://doi.org/10.1056/NEJMoa2015301
17. S. Mulangu, L.E. Dodd, R.T. Davey Jr., et al., A randomized, controlled trial of Ebola virus disease therapeutics. *N. Engl. J. Med.* 2019; 381(24):2293–2303. https://doi.org/10.1056/NEJMoa1910993
18. T.I. Hariyanto, F. Kwenandar, K.V. Japar, et al., The effectiveness and safety of remdesivir for the treatment of patients with COVID-19: a systematic review and meta-analysis. Anti-Infect. Agents. 2021; 19(3):333–340. https://doi.org/10.2174/22113533MTEwgNTYp4
19. G.A. Maldarelli, M. Savage, S. Mazur, et al., Remdesivir treatment for severe COVID-19 in third-trimester pregnancy: case report and management discussion. *Open Forum Infect. Dis*. 2020; 7(9):ofaa345(9).
20. C.D. Spinner, R.L. Gottlieb, G.J. Criner, et al., Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020; 324(11):1048–1057. https://doi.org/10.1001/jama.2020.16349
21. J. Jacobson, K. Antony, M. Beninati, et al., Use of dexamethasone, remdesivir, convalescent plasma and prone positioning in the treatment of severe COVID-19 infection in pregnancy: a case report. Case Rep. *Womens Health.* 2021; 29(29):e00273. https://doi.org/10.1016/j.crwh.2020.e00273