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Impact of COVID-19 on pregnant women in South Korea: Focusing on prevalence, severity, and clinical outcomes

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\textbf{A B S T R A C T}

\textit{Background:} In the era of coronavirus disease 2019 (COVID-19) pandemic, there is a paucity of information regarding actual prevalence of COVID-19 in pregnant women compared to non-pregnant women. The purpose of this study was to investigate the prevalence of COVID-19 infection and clinical outcome in pregnant women and non-pregnant women.

\textit{Methods:} This is a nationwide cross-sectional study in South Korea between January 2020 and February 2021 using the claim database. The primary outcome was the prevalence of COVID-19 in pregnant women, and the secondary outcome was the occurrence of severe COVID-19 illness among infected patients. Severity of COVID-19 was classified into four categories according to WHO ordinal scale.

\textit{Results:} The prevalence of COVID-19 infection was lower in pregnant women than non-pregnant women aged 20–44 (0.02% vs. 0.14%, \textit{p} < 0.0001). However, among COVID-19 positive women at age 20–44, pregnant women were at higher risk of oxygen therapy after hospitalization (score 4 in WHO ordinal scale: 6.4% vs. 1.6%, \textit{p} < 0.05). There were no deaths or hospitalized severe disease in pregnant women with COVID-19, although the majority of them (96.2%) were admitted to hospital. On the other hand, 42.3% of non-pregnant women at 20–44 age were admitted to hospital and 0.04% of them died and 0.1% had hospitalized severe disease.

\textit{Conclusions:} The prevalence of COVID-19 infection in pregnant women was lower than non-pregnant women in Korea, resulting in relatively small cases of fatality. It has implications that public health policy, such as an effective response to COVID-19 and a powerful preemptive strategy for pregnant women, can lower risk of COVID-19 infection and better clinical outcomes in pregnant women with COVID-19.

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\textbf{Introduction}

We are living the era of coronavirus disease 2019 (COVID-19) pandemic since 2019. According to WHO Coronavirus (COVID-19) Dashboard, as of 1 September 2021, there have been 217,558,771 coronavirus infected cases of COVID-19 and 527,942 new cases were reported to WHO [1]. Pregnant women are no exception to COVID-19 infection. According to WHO collaborating centre for global women's
health’s analysis, the prevalence of COVID-19 in pregnant women was 10% among the participants who admitted for any reasons [2].

Because of physiologic changes in both respiratory and immune systems, it is well known that pregnant women are susceptible [3] and prone to develop severe respiratory infection [4]. With enlarged uterus as pregnancy progressed, diaphragm is elevated, and angle of rib cage is increased [5]. With anatomical adaptation, tidal volume and minute oxygen uptake increase and functional residual capacity and total pulmonary resistance decreases. This physiological change of pregnant women body can decrease the capacity of compensation for pregnant women with some pulmonary complications [6].

It has been reported that the clinical course of the COVID-19 infection in pregnant women is worse than non-pregnant women with slower recovery [7]. Some reported that the severe COVID-19 infection rate in pregnant women was 70% higher than non-pregnant women of the same age [8]. In 2020, Morbidity and Mortality Weekly Report published by US Department of Health and Human Services/Centers for Disease Control and Prevention reported that pregnant women with coronavirus disease 2019 (COVID-19) might be at increased risk for severe illness compared with non-pregnant women [9].

Until now, there is a paucity of information regarding the actual prevalence of COVID-19 infection in pregnant women compared to non-pregnant women. Previous studies from United States, United Kingdom, and other countries throughout the world reported relatively higher prevalence of COVID-19 among pregnant women (ranged from 1·3%~30·74% [10,11]). However, the studies focused only on pregnant women, limiting comparability of actual prevalence between pregnant and non-pregnant women. In South Korea, National Health Insurance Service (NHIS) is a single healthcare insurer, enabling accurate nationwide estimation of disease prevalence.

This study was designed to investigate whether the prevalence and clinical outcome of COVID-19 infection in pregnant women differed from those in non-pregnant women. We compared the following outcomes between pregnant and non-pregnant (1) the prevalence of COVID-19 infection in the entire population of South Korea and women aged 20–44, and (2) the prevalence of severe or fatal COVID-19. In addition, we analyzed the hospitalization rate to determine the healthcare utilization patterns of COVID-19 infected pregnant women.

**Material and methods**

**Data sources and study design**

This is nationwide cross-sectional study using claims data provided by the Health Insurance Review and Assessment Service (HIRA). Under the universal health coverage, HIRA database contains medical use, diagnosis and treatment history for COVID-19 patients and pregnant women. Two cohorts were constructed. Cohort 1 was designed to compare prevalence of COVID-19 infection and occurrence of severe COVID-19 illness in pregnant women to the risks in non-pregnant women among COVID-19 patients. Cohort 2 was constructed to compare risks of obstetric complication in pregnant women with COVID-19 to the risks in pregnant women without COVID-19.

**Study population**

COVID-19 patients and pregnant women were defined based on the International Classification of Disease-10th Revision and Fee-for-service billing codes in South Korea (Appendix Table). For cohort 1, COVID-19 patients were defined as those who were diagnosed with and treated for COVID-19 (U07.1) from January 2020 to February 2021 (Fig. 1). The total number of COVID-19 patients was 75,805, and we divided female COVID-19 patients (n = 39,874) into pregnant women group (n = 78) and non-pregnant women group (all ages: n = 39,796 and 20–44 age: n = 11,463). For cohort 2, we selected pregnant women whose pregnancy was terminated by delivery between January 2020 and February 2021 (n = 313,716). Pregnant women with COVID-19 were defined as those which were infected COVID-19 during pregnancy. There were 73 pregnant women with COVID-19 and 313,643 pregnant women without COVID-19.

**Data collection**

Sex, age insurance type, region, underlying disease, sites for treatment, length of stay, severity of COVID-19 infection were extracted from the claim data for cohort 1. Insurances were divided into National Health Insurance (NHI) beneficiaries and Medical aid (MA) recipients. Regions were classified into the Seoul metropolitan area, Daegu and Gyeongsangbuk province, and other areas, according to the COVID-19 epidemic areas in South Korea. Underlying diseases includes hypertension, congestive heart failure, cerebrovascular disease, liver disease, renal
disease, chronic pulmonary disease, defined by ICD-10 codes (Appendix Table). Sites for treatment were classified into in-hospital admission and community treatment center where asymptomatic or mild COVID-19 patients were monitored. Length of stay was calculated by difference between the start date and the end date of the treatment related to COVID-19 infection. Severity of COVID-19 infection was classified into ambulatory state (scale 1), hospitalized mild disease (scale 3–4), hospitalized severe disease (scale 5–7) and dead (scale 8) using the WHO’s ordinal scale [12]. We defined patients in ambulatory state as those who were treated in community treatment centers. Among WHO ordinal scale, limitation of activities (scale 2) were not able to be determined. For cohort 2, maternal obstetric complication included preeclampsia, eclampsia, gestational hypertension, gestational diabetes mellitus, placenta previa, abruptio placenta, obstructed labor, preterm delivery, acute pyleonephritis, perineal laceration, obstetric hemorrhage, and fetal stress, defined by ICD-10 codes (Appendix Table).

Statistical analysis

Frequency analyses were conducted to identify baseline characteristics, severity of COVID-19 infection, and maternal obstetric complication. The prevalence was calculated by dividing the number of COVID-19 patients by whole number of NHI beneficiaries including medical aid recipients. Chi-square tests, Fisher’s exact tests and t-tests were performed to assess the difference between pregnant women with COVID-19 and other groups. All statistical tests were two sided and a p < 0.05 value was considered a statistically significant value. SAS Enterprise guide 7.1 was used for all analyses. SAS Enterprise guide 7.1 was used for all analyses.

Results

Characteristics of pregnant / non-pregnant women with COVID-19

During the study period, there were 39,874 female with COVID-19 (all ages: n = 39,796 and 20–44 age: n = 11,463) and 78 pregnant women with COVID-19. All pregnant women with COVID-19 were at the age of 20–44. Compared to non-pregnant women at 20–44 age and the general population, pregnant women with COVID-19 were less likely to be MA recipients and have underlying diseases, and more likely to live in Daegu and Gyeongsangbuk province. There was no significant difference in baseline characteristics between pregnant women and non-pregnant women at 20–44 age (Table 1).

Prevalence of COVID-19 infection in pregnant / non-pregnant women

Among a total of 52,870,968 people in South Korea, 75,805 (0.14%) were diagnosed as COVID-19 between January 2020 and February 2021. The prevalence of COVID-19 infection was lower in pregnant women (0.02%) than non-pregnant women at all ages (0.15%) and non-pregnant women aged 20–44 (0.14%) (p < 0.001). (Fig. 2).

Severity of COVID-19 in pregnant / non-pregnant women

The majority of pregnant women with COVID-19 (96.2%) were admitted to hospital. On the other hand, 42.3% of non-pregnant women with COVID-19 at 20–44 age were admitted to hospital. Mean length of stay in pregnant women with COVID-19 was shorter (11.7 days ± 6.4 days) than non-pregnant women of all-ages (mean 14.6 days ± 9.9 days) and non-pregnant women aged 20–44 with COVID-19 (13.6 days ± 9.2 days) (p < 0.001).

Among COVID-19 infected women, scale 3 (No oxygen therapy, 89.7% vs. 40.5%, p < 0.001) and scale 4 (Oxygen by mask or nasal prongs, 6.4% vs. 1.6%, p < 0.05) were significantly higher in pregnant women than non-pregnant women aged 20–44 (Table 2). There were no deaths or hospitalized severe disease (scale 5–8) in pregnant women with COVID-19, whereas 0.04% of non-pregnant women at 20–44 age died and 0.1% of them had severe COVID-19 illness.

Obstetrical complications

Then we compared maternal obstetric complication in cohort 2. Compared with pregnant women without COVID-19, the pregnant women with COVID-19 were more likely to be undergone cesarean...
section (78-1% vs 54-7%, p < 0.001). Majority of pregnant women delivered live birth in both groups, and the prevalence of obstetrical complications, such as preeclampsia, eclampsia, gestational hypertension, gestational diabetes mellitus, placenta previa, abruptio placentae, obstructed labor, preterm delivery, acute pyelonephritis, perineal laceration, and fetal distress showed no statistically significant difference between two groups, except lower risk of obstetric hemorrhage in pregnant women with COVID-19 (Table 3).

**Discussion**

The results of this study, which analyzed the prevalence of COVID-19 in pregnant women and clinical outcome through the HIRA database in South Korea, showed that 1) The prevalence of COVID-19 infection was lower in pregnant women than non-pregnant women; 2) Among COVID-19 infected women at age 20–44, pregnant women was at higher risk of oxygen therapy after hospitalization. However, there were no cases of hospitalized severe disease or death in pregnant women with COVID-19.

Previous studies reported relatively higher prevalence of COVID-19 infection among pregnant women all over the world, ranging 1-3% –30-74% [10,11]. In one study from the United States, tests of all pregnant women who admitted to two New-York based delivery hospitals confirmed 15-6% of COVID-19 infection, including 1-9% of symptomatic pregnant women and 13-7% of asymptomatic COVID-19 infection [13]. This prevalence was supposed to be much higher than the prevalence in general population, which was 0.16% in New York City [14], although these results are derived from different center and different periods. In another study from a large delivery hospital in United Kingdom also reported higher prevalence of COVID-19 infection (one out of 10 pregnant women) [15] and other reported the range of 1-3%–30-74% [10,11] of COVID-19 infection among pregnant women in various countries.

The result from previous studies is different from the result of the current study, as we showed relatively lower incidence of COVID-19 in pregnant women (0.02%). The higher prevalence in pregnant women from previous studies might be partially because of higher chance of nosocomial infection during frequent antenatal visits. The nosocomial infection of COVID-19 was reported in range of 3-7%-44% [16,17] among COVID-19 patients depending on the hospital reported. In spite of social distancing policies, pregnant women are tended to be exposed to people in hospital and might increase the risk of transmission as they regularly visit hospitals for antenatal care including fetal surveillance. However, the nosocomial infection risk is thought to be lower in South Korea than in other countries. The recent two-week nosocomial infection announced by South Korea Centers for Disease Control and Prevention(KCDC) was relatively low at about 1% (as of September 3, 2021) [18] among newly diagnosed COVID-19 infection.

It was reported that clinical outcome and disease severity of COVID-19 infected pregnant women were not significantly different from those of non-pregnant women in early study [19]. However, recent studies reported that pregnant women were at higher risk of severe COVID-19 illness than non-pregnant women, such as maternal death, intubation, and intensive care unit admissions.

**Table 2**

Severity of COVID-19 infection in pregnant / non-pregnant women.

| Sites for treatment | COVID-19 patients (n = 75,805) | Female COVID-19 patients (n = 39,874) | Pregnant women (Group 3) (n = 78) | p-valuea (2 vs 3) | p-valueb (1 vs 3) |
|--------------------|-------------------------------|--------------------------------------|----------------------------------|------------------|------------------|
| N                  | %                | n                  | %            | n                  | %            | n                  | %            | n                  | %            | n                  | %            | n                  | %            |
| In-hospital admission | 44,837 | 59.2 | 23,843 | 59.9 | 4844 | 42.3 | 75 | 96.2 | < 0.001 | < 0.001 |
| Community treatment center | 36,370 | 48.0 | 18,643 | 46.9 | 7442 | 64.9 | 4 | 5.1 | < 0.001 | < 0.001 |
| Length of stay 14.3 | 9.7 | 14.6 | 9.9 | 13.6 | 9.2 | 11.7 | 6.4 | < 0.001 | < 0.001 |
| Severity(WHO ordinal scale) | | | | | | | | | | | |
| Ambulatory state | | | | | | | | | | | |
| 1: Non hospitalized | 30,960 | 40.8 | 15,194 | 40.1 | 6617 | 57.7 | 3 | 3.9 | < 0.001 | < 0.001 |
| Hospitalized mild disease | 34,231 | 45.2 | 18,635 | 46.8 | 4644 | 40.5 | 70 | 89.7 | < 0.001 | < 0.001 |
| 3: No oxygen therapy | 7334 | 9.7 | 3705 | 9.3 | 181 | 1.6 | 5 | 6.4 | < 0.05 | 0.56 |
| 4: Oxygen by mask or nasal prongs | 1148 | 1.5 | 441 | 1.1 | 15 | 0.1 | – | – | 1.00 | 1.00 |
| Hospitalized severe disease | 340 | 0.5 | 140 | 0.4 | 1 | 0.01 | – | – | 1.00 | 1.00 |
| 5: Non-invasive ventilation or high-flow oxygen | 78 | 0.1 | 31 | 0.1 | – | – | – | – | 1.00 | 1.00 |
| 6: Intubation and mechanical ventilation | | | | | | | | | | | |
| 7: Ventilation+additional organ support (CRRT, ECMO) | | | | | | | | | | | |
| 8: Death | 1714 | 2.3 | 895 | 2.3 | 5 | 0.04 | – | – | 1.00 | 0.43 |

COVID-19, coronavirus disease 2019

CRRT, Continuous Renal Replacement Therapy, ECMO: Extracorporeal membrane oxygenation

*a* Chi-square tests and Fisher’s exact tests and t-test were performed.

*b* COVID-19 patients might have been treated both in hospitals and community treatment centers or in either of the sites.

*c* Scale was assigned to a patient according to the most severe condition during a treatment period.
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Table 3 Pregnancy outcome / obstetrical complications of pregnant women with / without COVID-19.

|                      | Pregnant women with COVID-19 (n = 75) | Pregnant women without COVID-19 (n = 313,643) | p-value* |
|----------------------|--------------------------------------|---------------------------------------------|----------|
| Result of childbirth |                                      |                                             |          |
| Live birth           | 73                                   | 312,888                                    | 99.8     |
| Stillbirth           | 0                                    | 755                                         | 0.2      |
| Cesarean section     | 57                                   | 171,470                                    | 54.7     |
| Vaginal delivery     | 16                                   | 142,173                                    | 45.3     |
| Type of delivery     |                                      |                                             |          |
| Cesarean section     | 57                                   | 171,470                                    | < 0.001  |
| Vaginal delivery     | 16                                   | 142,173                                    |          |
| Obstetrical          |                                      |                                             |          |
| complications        |                                      |                                             |          |
| Preeclampsia         | 1                                    | 1.4                                        | 1.8      |
| Eclampsia            | 0                                    | 162                                        | 0.1      |
| Gestational          | 4                                    | 10,100                                     | 3.2      |
| Hypertension         | 13                                   | 17.8                                       | 18.4     |
| Gestational diabetes mellitus | 13 | 17.8 | 18.4 | 1.0 |
| Placenta previa      | 5                                    | 6.9                                        | 3.1      |
| Abruptio placenta    | 0                                    | 1505                                       | 0.5      |
| Obstructed labor     | 6                                    | 8.2                                        | 11.3     |
| Preterm delivery     | 4                                    | 5.5                                        | 2.3      |
| Acute                | 17                                   | 22.3                                       | 25.1     |
| Pyleonephritis       | 1                                    | 1.4                                        | 4.0      |
| Perineal laceration  | 4                                    | 5.5                                        | 15.0     |
| Obstetric hemorrhage | 3                                    | 4.1                                        | 16,410   |
| Fetal stress         |                                      |                                             | 5.2      |
| COVID-19 infection   |                                      |                                             | 1.0      |

COVID-19, coronavirus disease 2019

* Chi-square tests and Fisher’s exact tests were performed

According to the results of our study, the severity of COVID-19 was higher in pregnant women like previous studies. However, there were no cases of death or hospitalized severe diseases in pregnant women with COVID-19, probably because of small number of cases of COVID-19 in pregnant women. Lower prevalence of COVID-19 infection and low proportion of death or hospitalized severe diseases of COVID-19 illness among pregnant women in South Korea might be explained by effective response to COVID-19 and strong preemptive strategy for pregnant women. From the early stage of outbreak, South Korea has employed a 3 T (Testing-Tracking-Treatment) strategy to prevent and combat the spread of COVID-19. Early detection of COVID-19 through massive diagnostic testing, contact tracing and treatment of confirmed cases were effective response package [22,23]. As a result, South Korea avoided a large COVID-19 outbreak and prevented collapse of health care system.

Furthermore, South Korea adopted more protective approach for high risk groups including pregnant women, the elderly and vulnerable people than for other population. All of COVID-19 patients are treated in community treatment centers or hospitals according to the patient’s condition. Asymptomatic or mild COVID-19 patients were assigned to community treatment centers, and moderate or severe patients were treated in hospitals. The recommended treatments for COVID-19 infected pregnant women is not much different from those for general population [24,25]. After confirmation of COVID-19 infection, assessment about pregnancy trimester [26], maternal condition, symptoms and severity of the disease is needed. Based on the assessment, physicians can decide treatments and medications such as oxygen supply therapy, steroids, tocilizumab, and remdesivir [25]. The low molecular weight heparin (LMWH) for venous thromboembolism (VTE) prevention of pregnant women may be the difference. Despite the similar recommended treatments, hospitalization was the first option to be considered for pregnant women with COVID-19 regardless of severity of infection according to government’s guideline [23,27]. The current study also showed that 96.2% of pregnant women with COVID-19 were monitored and treated more intensively and cautiously in the hospitals. The effective response to COVID-19 and the powerful preemptive strategy for pregnant women with COVID-19 contributed to lower risk of COVID-19 infection and better clinical outcomes in pregnant women with COVID-19 in South Korea.

Previous studies showed that the COVID-19 infected pregnant women had higher risk of obstetrical complications such as cesarean section rate, preterm birth, and NICU admission rate [21,28]. This findings suggested that the obstetrical outcome could be affected by the severity of COVID-19 infection [29]. In the current study, rate of cesarean section of pregnant women with COVID-19 was higher than pregnant women without COVID-19 infection. Several studies showed high cesarean section rate in pregnant women with COVID-19 (93% in China [19], 90.2% in Italy [30]). Although there is no evidence about cesarean section in COVID-19 infected pregnant women can result in better obstetric outcomes such as vertical transmission than vaginal delivery [31], the reason for higher cesarean section rate in pregnant women with COVID-19 is thought to be due to anxiety or fear about new infectious diseases [30,32]. In other obstetrical complications had no significant difference, which is not consistent with findings of other studies [21]. However, pregnant women with COVID-19 showed less obstetrical hemorrhage than pregnant women without COVID-19. Several studies reported changes of coagulation state and elevated risk of thromboembolic events in pregnant women with COVID-19 [33,34]. This might be the reason for less obstetrical hemorrhage in pregnant women with COVID-19 in spite of higher rates of cesarean section, which is known to have higher blood loss than vaginal delivery.

There was no clear evidence regarding effects of vaccination during pregnancy in early study [35]. However, recent studies reported that the effectiveness of COVID-19 vaccination for pregnant women was similar to that of general population, and the risk of COVID-19 infection was significantly lower in pregnant women who were vaccinated when compared with those not vaccinated [36,37]. A mass vaccination program was launched in late February 2021 in South Korea. Vaccination for residents aged 49 and under started in August 2021, and vaccination for pregnant women was started in October 2021. Therefore, effect of vaccination was limited in our study which analyzed the data up to February 2021. Further research would be necessary to study effects of vaccination on pregnant women herself and fetus.

The current study had strength and limitation. The major strength of this study is analyzing the nationally representative data. The HIRA database used in this study contains information on all claims including any diagnosis, treatments and procedures for approximately 52 million Koreans. Analyzing nationwide database enabled accurate estimation and direct comparison of prevalence of COVID-19 infection in women according to pregnancy status. Limitation of this study is lack of clinical information in the claim data. To address this issue, WHO’s ordinal scale for clinical im.

Conclusions

In conclusion, the prevalence of COVID-19 infection among pregnant women in South Korea was lower than that of non-pregnant women. There were no COVID-19 related deaths or hospitalized severe disease in pregnant women with COVID-19. They also had a higher rate of cesarean section than pregnant women without COVID-19, but they did not show higher prevalence of obstetric complication. It has implications that even though pregnant women with COVID-19 are considered as vulnerable population, the risk of pregnant women itself can be reduced by public health policy such as effective response to COVID-19 and a powerful preemptive strategy for pregnant women.
The study and the methodology were conceived by all authors. Yeonmi Choi and Dokyoung Lee led the data analysis and Yeonmi Choi, Heejin Lee, Ji Hoi Kim, Eun Saem Choi, Young Mi Jung, Ji Yoon Lee, Yeonmi Choi, Heejin Lee, Ji Hoi Kim, Eun Saem Choi, Young Mi Jung, Ji Yoon Lee, Youn Myeong Do, Jinwoo Lee, Pyoeng Gyun Choe, Chan-Wook Park, Jong Shin Park, Jong Kwan Jun, Seung Mi Lee, and Jin Yong Lee interpreted the results. All authors collaborated on writing the paper. Seung Mi Lee, So Hee Kim, Hyejin Lee, Ji Hoi Kim, Eun Saem Choi, Young Mi Jung, Ji Yoon Lee, Youn Myeong Do, Jinwoo Lee, Pyoeng Gyun Choe, Chan-Wook Park, Jong Shin Park, and Jong Kwan Jun provided intellectual contributions and critically revised the manuscript. All authors approved the final version.

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Ethical statement

This study was approved by Institutional review board of the Health Insurance Review and Assessment Service (2021-099-001).

Declaration of interests

The authors declare that there are no conflicts of interests.

Data Availability

All data used in this study are publicly available after obtaining permission for use from the Health Insurance Review and Assessment Service (HIRA). The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted, and all discrepancies from the study as planned have been explained.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.01.004.

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