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RESEARCH ARTICLE

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COVID-19 Infection and Women's Health; which Women are More Vulnerable in Terms of Gynecological Health?

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ABSTRACT

Research question: Given gender-specific differences and ACE2 commonly expressed in the ovaries and uterus, it may be important to know which women are at greater risk of COVID-19 infection. Therefore, this study sought to determine which women are more affected by COVID-19 infection, especially in terms of gynecological pathologies.

Design: This retrospective and descriptive study examined the effect and course of COVID-19 in terms of gynecological pathologies in a total of 380 women of reproductive age without systemic disease. General demographics, obstetric and gynecological conditions and parameters related to COVID-19 were evaluated. All parameters were compared for three groups defined on the basis of COVID-19 severity (mild, moderate and severe).

Results: A total of 380 women with a mean age of 35.39 ± 8.94 were included in the study. The mean Body Mass Index (BMI) of the women was 24.35 ± 4.53. The proportion of women with at least one pregnancy history was 69.2%. The mean gravidity of the women was 1.47 ± 1.34 and the parity was 1.16 ± 1.02. Of the women, 112 (29.5%) mild, 207 (54.5%) moderate and 61 (16.0%) severe cases of COVID-19 were seen. The mean age and median BMI of the women were similar in all three groups (p=0.163, p=0.127, respectively). Severe disease rates (29.5%) were significantly higher in women with 2 or more cases of COVID-19 than mild disease (14%) (p=0.018). Severe disease rates (57.4%) in women with at least one pregnancy history were statistically significantly lower than mild disease rates (78.6%) (p=0.010). The median parity number was significantly higher in the mild disease group than in the moderate disease group (p=0.021). The most common benign gynecological pathology in women was chronic urinary tract infection (13.2%). Other common pathologies were chronic vaginal infection (12.6%) and Polycystic Ovary Syndrome (PCOS) (11.6%). A history of chronic urinary tract infection was statistically significantly higher in the severe disease group (24.6%), mild (8.9%, p=0.015) and moderate (12.1%, p=0.024) disease groups. PCOS, endometriosis (6.3%), Abnormal Uterine Bleeding (AUB) (8.4%) and hormone therapy history (8.2%) were found to be higher in severe disease groups, although not statistically significant (p=0.596, p=0.074, p=0.305, p=0.059, respectively). The history of leiomyoma (7.1%) was higher in the mild and moderate disease groups than in the severe disease group, but it was not statistically significant (p=0.794). Benign gynecological operation history (31.3%) was significantly higher in mild (36.6%, p=0.007) and moderate (33.3%, p=0.007) disease groups than in the severe group (9, 14.8%).

Conclusions: Certain obstetric and gynecological conditions are thought to affect COVID-19 susceptibility and severity in women without systemic disease.

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Introduction

Coronaviruses are a large family belonging to the *Coronaviridae* family known to cause respiratory infections in humans and animals [1]. After the first pneumonia case was reported in Wuhan in December 2019, the virus, which had spread rapidly all over the world and had a high risk of death, was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2) or COVID-19 virus by the WHO. In many recent studies, the general epidemiology of COVID-19 patients, as well as their clinical and laboratory features have been reported [2]. Globally, as of May 03, 2023, 765,222,932 confirmed cases of COVID-19 have been reported to the WHO, including 6,921,614 deaths [3].

For COVID-19, age, gender, metabolic, cardiovascular and endocrine diseases may be risk factors for more frequent and severe episodes of the disease. Many epidemiological studies have shown that age and gender are important prognostic factors for COVID-19 [4]. In many countries, men with laboratory-confirmed COVID-19 have been found to have higher rates of admission to intensive care units, serious sequelae, and even death than women. [5,6]. The greater susceptibility to severe COVID-19 in men, regardless of age, has led to questions with regard to the potential effects of sex hormones on Angiotensin-Converting Enzyme 2 (ACE2) expression. Immunological and hormonal differences may explain this difference in sensitivity between the sexes. It is already known that the SARS-CoV-2 Spike (S) glycoprotein must bind to the host receptor ACE2 for viral entry. In addition, the host Transmembrane Protease Serine Protease 2 (TMPRSS2) has been shown to induce a conformational change that subsequently enables the fusion of viral and host cell membranes [7,8]. ACE2 and TMPRSS2 may be key indicators of whether a particular cell type is susceptible to viral infection [9]. It has been shown that ACE2 has a dysmorphic sex pattern and increased kidney and lung ACE2 protein expression in male mice compared to that in females [10]. It has also been reported that TMPRSS2 protein expression is upregulated by androgens, as in ACE 2 [11]. These findings may indicate that androgens increase COVID-19 susceptibility and severity in men. In addition, it has been shown that ACE2 is also expressed in stroma and granulosa cells in immature rat ovaries [12]. ACE2 has regulatory effects on follicular development, ovulation and luteal functions in the ovaries as well as on the uterine endometrial tissue [13,14]. This could mean that the ovaries and uterus may also be the target of SARS-CoV-2 and alter susceptibility to COVID-19 in some gynecological pathologies.

On the other hand, females generally develop higher immune responses than males. Attempts have been made to explain this *via* chromosomal and hormonal factors [15]. The powerful immune modulators of estradiol and possibly progesterone may protect women [16]. Estrogen receptors are expressed on most immune cells. The anti-inflammatory effects of estrogen have been demonstrated in most experimental human or rodent models [17,18]. Even in viral infections, it has been shown that estrogen prevents the cytokine storm in the lungs and protects them from fatal pneumonia [19]. Progesterone, another immunomodulatory hormone, has been shown in experimental studies to support the repair and rapid healing of tissue damage caused by viral effects, together with its anti-inflammatory properties [20].

Varying concentrations of sex steroids, which are potent immunomodulatory, in different gynecological pathologies may affect the immune response and inflammatory outcomes. In addition, gynecological chronic inflammatory diseases in women may impair their immune response, making them more susceptible to COVID-19 disease and worsening outcomes. Many studies have attempted to evaluate the effects of COVID-19 in terms of female fertility. As far as we know, there is no study in the literature evaluating the susceptibility and severity of COVID-19 in women in terms of many gynecological conditions. The aim of this study is to evaluate the possible relationship between the frequency and severity of COVID-19 and gynecological diseases or conditions that may cause hormonal changes in women, who have had COVID-19.

Materials and Methods

Study design

This single-center, retrospective and descriptive study included women aged 18-49 years with confirmed COVID-19 infection. A total of 670 women with COVID-19, who applied to the Gynecology and Obstetrics Clinic of Başkent University Konya Practice and Research Hospital between March 2021 and September 2022 for a normal gynecological examination, were invited to participate in the study. Pre-prepared detailed clinical history forms, including general demographic questions, obstetric and gynecological history questions and questions about the COVID-19 process, were distributed to the women and women, who agreed to participate in the study, were asked to fill out these forms. After the study was accepted by the Republic of Turkey, Ministry of Health General Directorate of

Health Services (2022-02-02T14_15_43), it was approved by the Başkent University Medical and Health Sciences Research Board (KA22/144 March 2022).

Participants: A total of 520 women agreed to participate in the study. All enrolled patients were confirmed to have COVID-19 *via* Polymerase Chain Reaction (PCR) tests. Patients with serious systemic diseases such as diabetes, cardiovascular disease, obstructive pulmonary disease, acquired or congenital coagulation disorder, liver and kidney disease, patients with gynecological cancer, hysterectomy, bilateral oophorectomy and patients receiving chemotherapy or radiotherapy affecting ovarian functions were excluded from the study. Pregnant or breastfeeding women with COVID-19 were also excluded from the study. After excluding all diseases and conditions that might have affected the severity of COVID-19, a total of 380 patients were evaluated for the study.

Data collecting: Detailed clinical-story forms prepared with the support of the Public Health Department of our university were presented to the patients in a quiet polyclinic room accompanied by a nurse. After the nurse gave the necessary explanations for the questions on the forms, the women completed the forms within 10 minutes. The questions in the data forms were divided into three categories. General information such as age, height, weight, systemic disease and surgery history, alcohol and smoking were in the first category, detailed obstetric history and gynecological conditions were in the second category and information about the COVID-19 process was in the third category. With respect to obstetric and gynecological history, gravida, parity, abortion, adnexal and uterine pathologies (Polycystic Ovary Syndrome (PCOS), leiomyoma, endometriosis, endometrioma, abnormal uterine bleeding, chronic vaginal and urinary tract infection), hormonal contraceptive use, gynecological cancer and history of surgery was questioned. A pregnancy history was defined as having had at least one live pregnancy. Women were asked separately about the prresence of gynecological diseases such as PCOS, leiomyoma and endometriosis and were asked to provide either a negative or positive repsonse. Cesarean section, myomectomy and simple ovarian cyst excisions were included in the definition of benign gynecological operations. The definition of chronic urinary tract infection was defined as infections that did not respond to treatment and often recurred. Having 4 or more vaginal infections per year was defined as chronic vaginal infection. Abnormal uterine bleeding was defined as irregular heavy and prolonged bleeding episodes not related to pregnancy. For COVID-19 characteristics, women were asked about the course of the disease (mild, moderate and severe) and vaccination status. They were also asked about the number of times they had had COVID-19, how often they had been hospitalized or admitted to intensive care. In terms of clinical manifestations, mild disease was defined as asymptomatic or mild fever, malaise, myalgia, headache and sore throat; moderate disease was defined as fever, cough, arthralgia and mild dyspnoea; and severe disease was defined as severe dyspnoea and tachypnoea (respiratory rate >30/min) in addition to other manifestations [5].

Outcome measures: All parameters were compared for the three groups (mild, moderate and severe) defined for COVID-19 severity. The main purpose was to evaluate in general whether any gynecological disease or condition affects the frequency and severity of COVID-19 in terms of female gender.

Statistical analysis: SPSS 25.0 (IBM Corporation, Armonk, New York, USA) and Python programs were used in the analysis of the variables. The conformity of univariate data to the normal distribution was evaluated with the Shapiro-Wilk Francia test and the homogeneity of the variance was evaluated with the Levene test. The Monte Carlo simulation and Kruskal Wallis H Test were used to compare more than two independent groups with each other in terms of quantitative variables and the Dunn's test was used for post-hoc analysis. The Fisher Freeman Halton test and Chi-squared test were used to compare categorical variables with each other and the Benjamin-Hochberg test was used for post-hoc analysis. In the tables, quantitative variables were expressed as median (minimum/ maximum), while categorical variables were shown as n (%). Variables were analyzed at a 95% confidence level and a p-value of less than 0.05 was considered significant.

Results

Patient demographics

A total of 380 patients were included in the study. The general descriptive evaluations of the participants are given in Table 1. The clinical characteristics based on disease severity in women with COVID-19 are set out in Table 2. The median age of the women was 35 and the median Body Mass Index (BMI) was 24.88. Median age and BMI values were similar in all three groups. The alcohol and cigarette usage rates of women were 18.2% (69) and 18.4% (70), respectively. Alcohol and smoking rates did not differ significantly between mild, moderate and severe disease groups (p=0.751 and p=0.339, respectively).

COVID-19 characters: Women with COVID-19 were evaluated in three groups according to disease se-

verity. The rates of mild disease were 29.5% (112), moderate disease rates were 54.5% (207) and severe disease rates were 16.0% (61). Of the women, 92.9% (353) were vaccinated, 54.7% (208) received antiviral treatment, 9.0% (34) were hospitalized and 1.0% (4) stated that they had received treatment in the intensive care unit. In addition, 81.6% (310) of women stated that they had had COVID-19 only once, while 18.4% (70) stated that they had had COVID-19 two or more times. Vaccination rates were similar in mild (93.8%), moderate (91.3%) and severe (96.7%) disease groups. Severe disease rates (29.5%, 18) were found to be significantly higher than mild (12.5%, 14) disease rates (p=0.018) in patients with two or more COVID-19 cases. The proportion of women receiving antiviral treatment was significantly higher in the severe (75.4%) disease group than in the mild (41.1%, p<0.001) and moderate (56%, p=0.010) disease groups. Naturally, hospitalization and intensive care treatment rates were significantly higher in severe disease groups (p<0.001, p=0.001) (Table 2).

Obstetric characteristics of women with COVID-19: The proportion of women with at least one pregnancy history was 69.2% (263). Pregnancy history was significantly different between mild (88, 78.6%), moderate (140, 67.6%) and severe (35, 57.4%) disease groups (p=0.012). In the severe disease group, the rates of pregnancy history were statistically significantly lower than in the mild disease group (p=0.010) (Table 2). The median (min-Q1-Q3-max) gravity, parity and abortion scores of the women were 1 (0-02-7), 1 (0-02-4) and 0 (0-00-5) respectively. In addition, the ectopic pregnancy rate was found to be 1.8% (7) (Table 1). Although the median gravida was highest in the mild disease group, it was not statistically significant between the groups (p=0.073). The median parity was highest in the mild disease group and was significantly higher than in the moderate disease group (p=0.021). The median number of abortions and ectopic pregnancy rates did not differ significantly between disease groups (p=0.838, p=0.999, respectively) (Table 2).

Gynecological characteristics of women with COVID-19: The most common benign gynecological pathologies in women were chronic urinary tract infection at 13.2% (50), chronic vaginal infection at 12.6% (48) and PCOS at 11.6% (44/336). Other benign gynecological disease histories were AUB, uterine leiomyoma, endometriosis and Human Papilloma Virus (HPV) infection and their incidence rates were respectively; 8.4% (32), 7.1% (27), 6.3% (24) and 3.7% (14) (Table 1). Except for chronic urinary tract infection, no significant difference was observed between the groups in terms of benign gynecological diseases. Chronic urinary tract infection rates were significantly different between mild (10, 8.9%), moderate (25, 12.1%) and severe (15, 24.6%) disease groups (p=0.011) and in the severe disease group, mild (p=0.015) and moderate (p=0.024) disease groups were found to be significantly higher. Although PCOS was seen at a higher rate in the moderate (12.6%) and severe (13.1%) disease groups than in the mild (8.9%) group, it was not found to be statistically significant (p=0.596). Endometriosis was found to be higher in the severe (13.1%) disease group than in the mild (4.5%) and moderate (5.3%) disease groups, although it was not statistically significant (p=0.074). Again, while the rate of severe disease (13.1%) was higher in women with a history of AUB than that in women in the mild (6.3%) and moderate (8.2%) disease groups, there was no significant difference between them (p=0.305). Interestingly, the rates of mild (9.8%) and moderate (7.2%) disease in women with leiomyoma were higher than the rates of severe (4.9%) disease, although not statistically significant (p=0.794) (Table 2). The proportion of women, who received hormonal therapy in the three months prior to COVID-19 was 8.2% (31) (Table 1). Although the rates of severe disease (13.1%) in women receiving hormone therapy were higher than in mild (10.7%) and moderate (5.3%) groups, it was not statistically significant (p=0.059) (Table 2). In addition, mild (36.6%, p=0.007) and moderate (33.3%, p=0.007) disease rates were significantly higher in women, who had benign gynecological operations, compared to those in the severe disease group (14.8%) (Tables 1 and 2).

Table 1. General demographic and clinical characteristics of women with COVID-19.

Charecteristics	Female Covid-19 patients
Age (years)	
Mean (SD.)	35.39 (8.94)
Median (min-Q1-Q3-max)	35 (18-28-42-49)
BMI, (kg/m^2)	
Mean (SD.)	24.35 (4.53)

Median (min-Q1-Q3-max)	23.88 (15.24-21.126.75-52.44)
Alcohol, n (%)	69 (18.2)
Smoking, n (%)	70 (18.4)
Reproductive history	
Pregnancy history, n (%)	263 (69.2)
Gravida	
Mean (SD.)	1.47 (1.34)
Median (min-Q1-Q3-max)	1 (0-02-7)
Parity	
Mean (SD.)	1.16 (1.02)
Median (min-Q1-Q3-max)	1 (0-02-4)
Abortion	
Mean (SD.)	0.21 (0.57)
Median (min-Q1-Q3-max)	0 (0-00-5)
Ectopic pregnancy, n (%)	7 (1.8)
Benign gynecological pathologies, n (%)	
Chronic urinary tract infection	50 (13.2)
Chronic vaginal infection	48 (12.6)
Polycystic Ovary Syndrome (PCOS)	44 (11.6)
Abnormal Uterine Bleeding (AUB)	32 (8.4)
Leiomyoma	27 (7.1)
Endometriosis/Adenomyosis	24 (6.3)
HPV infection	14 (3.7)
Gynaecological medical history, n (%)	
Gynecological surgery	119 (31.3)
Hormonal therapy	31 (8.2)
COVID-19 medical history, n (%)	
COVID-19 course	
Mild	112 (29.5)
Moderate	207 (54.5)
Severe	61 (16.0)
Vaccination	353 (92.9)
Number of COVID-19	
1 time	310 (81.6)
2 or more	70 (18.4)
Antiviral therapy	208 (54.7)
Hospitalization	34 (9.0)
Admission to the intensive care unit	4 (1.0)
Note: SD.: Standard deviation; min: Minimum; Q1: Percentile 25; Q3: Percentile 75; max: Maximum.	

Table 2. Comparison of all characters according to the severity of COVID-19.

	Mild (A) **(n=112)**	**Moderate (B)** **(n=207)**	**Severe (C)** **(n=61)**	**p**
Age, (years), median (min/max)	32 (18/46)	33 (18/47)	33,5 (18/49)	0.163[k]
BMI, (kg/m^2), median (min/max)	24.34 (18.29/42.24)	23.59 (15.76/52.44)	23.88 (15.24/35.99)	0.127[k]
Alcohol, n (%)	23 (20.5)	36 (17.4)	10 (16.4)	0.751[c]
Smoking, n (%)	21 (18.8)	34 (16.4)	15 (24.6)	0.339[c]

Pregnancy history[1], n (%)	88 (78.6)	140 (67.6)	35 (57.4)	0.012[c]
Gravida, median (min/max)	2 (0/6)	1 (0/7)	1 (0/5)	0.073[k]
Parity[2], median (min/max)	1.5 (0/3)	1 (0/4)	1 (0/4)	0.046[k]
Abortion, median (min/max)	0 (0/2)	0 (0/5)	0 (0/3)	0.838[k]
Ectopic pregnancy, n (%)	2 (1.8)	4 (1.9)	1 (1.6)	0.999[ff]
Chronic urinary tract infection3, n (%)	10 (8.9)	25 (12.1)	15 (24.6)[AB]	0.011[c]
Chronic vaginal infection, n (%)	11 (9.8)	25 (12.1)	12 (19.7)	0.164[c]
Polycystic Ovary Syndrome (PCOS), n (%)	10 (8.9)	26 (12.6)	8 (13.1)	0.596[c]
Abnormal Uterine Bleeding (AUB), n (%)	7 (6.3)	17 (8.2)	8 (13.1)	0.305[c]
Leiomyoma, n (%)	9 (8)	15 (7.2)	3 (4.9)	0.794[ff]
Endometriosis/Adenomyosis, n (%)	5 (4.5)	11 (5.3)	8 (13.1)	0.074[ff]
HPV infection, n (%)	5 (4.5)	6 (2.9)	3 (4.9)	0.607ff
Gynecological surgery[4], n (%)	41 (36.6)	69 (33.3)	9 (14.8)	0.008[c]
Hormonal therapy, n (%)	12 (10.7)	11 (5.3)	8 (13.1)	0.059[ff]
Vaccination, n (%)	105 (93.8)	189 (91.3)	59 (96.7)	0.359[ff]
2 or more COVID-19 infections[5], n (%)	14 (12.5)	38 (18.4)	18 (29.5)	0.021[c]
Antiviral therapy[6], n (%)	46 (41.1)	116 (56)	46 (75.4)	<0.001[c]
Hospitalization[7], n (%)	0 (0)	15 (7.2)	19 (31.1)	<0.001[c]
Admission to the intensive care unit[8], n (%)	0 (0)	0 (0)	4 (6.6)	0.001[ff]

Note: [k]Kruskal Wallis H Test (Monte Carlo); Post Hoc: Dunn's Test; [ff]Fisher Freeman Halton Test (Monte Carlo); Post Hoc: Benjaminini-Hochberg Test; [c]Chi Square Test (Monte Carlo); Post Hoc: Benjaminini-Hochberg Test; Bold values represent p<0.05, min: Minimum, max: Maximum.

1: P (A-C)=0.010; 2: P (A-B)=0.021; 3: (P (A-C)=0.015, P (B-C)=0.024); 4: (P (A-C)=0.007, P (B-C)=0.007); 5: P (A-C)=0.018; 6: (P (A-B)=0.011, P (A-C) ≤ 0.001, P (B-C)=0.010); 7: (P (A-B) ≤ 0.001, P (A-C) ≤ 0.001, P (B-C) ≤ 0.001); 8: (P (A-C) ≤ 0.001, P (B-C) ≤ 0.001).

Discussion

COVID-19 continues to present a serious global health problem. Studies examining the selective effects of COVID-19 in women are scarce. It has not yet been clarified whether there are factors that increase or decrease the susceptibility to COVID-19 in women other than chronic systemic diseases. In order to better understand the interaction between COVID-19 and the female gender, it is necessary to evaluate the risk factors well. In this study, it was aimed to evaluate the frequency and course of COVID-19 in terms of reproductive characteristics and gynecological diseases.

As expected, our study showed that women hospitalized, receiving intensive care support and receiving antiviral therapy had a more severe illness overall. Severe illness rates were found to be significantly higher than mild illness rates in women who had 2 or more episodes of COVID-19. The result of the study is consistent considering that recurrent virus infections and frequent exposure to the virus may lead to a higher COVID-19 viral load and thus worse clinical outcomes [21].

Although it has been stated in some studies that pregnancy is a risk factor for severe COVID-19, it has been reported that the risk of serious disease increases especially in the postpartum period, when estrogen and progesterone serum levels decrease [22,23]. Pregnancy is known to affect the immune system in a number of ways. Although the results of the studies are inconsistent, it is generally thought that there is a rather dynamic cooperative adaptation between the maternal and fetal immune systems rather than a particularly broad maternal immune suppression during pregnancy [24]. In our study, it was observed that women with at least one live pregnancy history had significantly milder disease and the probability of mild disease was higher as the parity number increased. While it is difficult to say with certainty that having a pregnancy history protects against severe COVID-19, it is important that a pregnancy history is an indicator of better health. Interestingly, the rates

of severe disease in women, who underwent gynecological surgery for benign reasons were significantly lower than the rates of mild and moderate disease. However, since cesarean section constitutes a large part of the benign gynecological surgery history in this study, the results are consistent with the results of the pregnancy history.

In the study, the most common urogenital pathology in women in the pre- COVID-19 period was chronic urinary tract infection. Chronic vaginal infection and PCOS were other common diseases. Interestingly, COVID-19 was significantly more severe in women with a history of chronic urinary tract infections. The urinary tract in men has proven to be a potential target for COVID-19. Studies have shown that COVID-19 infection significantly worsens stress incontinence and overactive bladder scores in both men and women and causes intense inflammatory cytokine release in the bladder [25,26]. While studies so far have shown that the urinary system is a target for COVID-19, our study has shown that urinary system diseases may be a risk factor. In addition, a history of chronic urinary or vaginal infections may indicate an above-normal immune system sensitivity. Although the mechanism is not clear, it is clear that there is an interaction between COVID-19 and the lower urinary tract.

Chronic inflammation and some endocrine conditions are more commonly associated with COVID-19. The susceptibility and severity of COVID-19 in gynecological diseases such as PCOS and endometriosis have been evaluated in some studies. Phelan et al. in their study examining the effects of COVID-19 on reproductive health in women, found that 7% of women with COVID-19 had PCOS and 6% had endometriosis [27]. The incidence of PCOS, which is the most common endocrine and metabolic problem in women of reproductive age, is 10%-15%. PCOS may increase susceptibility to COVID-19 due to impaired glucose tolerance, an increased prevalence of metabolic syndrome and hyperandrogenism. It has been reported that PCOS associated with hyperandrogenism leads to an almost 30% higher risk of COVID-19 infection than that in controls, independent of obesity [28]. In addition, it has been shown that polymorphisms in genes encoding proinflammatory cytokines are increased in women with PCOS [29]. In this context, PCOS may be a risk factor that predisposes women to severe COVID-19 due to both a low-level chronic inflammation state and its endocrine pattern. Several cross-sectional and large-scale studies have shown that women with PCOS are at greater risk for COVID-19 and that symptoms are more pronounced [30,31]. Endometriosis is one of the most common benign gynecological conditions in women of reproductive age. Changes in cell-mediated or humoral immunity in endometriosis, which is thought to be a chronic inflammatory disease, may affect susceptibility and severity to COVID-19 [32,33]. In a meta-analysis evaluating the relationship between endometriosis and COVID-19, it was emphasized that the risk of women with endometriosis contracting COVID-19 may increase, although it is not statistically significant [34]. In our study population, the rate of PCOS was 11.6% and the rate of endometriosis was 6.3% in women with COVID-19. Although not statistically significant, the rates of PCOS and endometriosis were higher in the severe COVID-19 group, consistent with the literature.

Low and altered expression of ACE2 and TMPRSS 2 in endometrial cells during the menstrual cycle may result in a lower overall risk for COVID-19 infection [35]. However, the expression of these receptors may be altered in cases of AUB and greater susceptibility to COVID-19 may occur. In addition, iron deficiency anemia is an important problem in these women and anemia may impair the immune response and increase susceptibility to infections [36]. It has been shown that endometrial hyperplasia, one of the most important causes of AUB, increases the risk of COVID-19 infection [37]. In our study, the rate of severe COVID-19 was found to be higher in women with a history of AUB, although it was not statistically significant.

In our study, the rates of severe disease were higher in women, who had received hormone therapy for contraceptive purposes in the three months prior to COVID-19 infection, although it was not statistically significant. In studies conducted with postmenopausal women, the anti-inflammatory effect of hormone therapy was reported in those who used transdermal estrogen instead of oral therapy [38]. In addition, oral estrogen therapy is known to increase inflammatory markers due to its liver first-pass effect [39]. Although our results are compatible with the literature in this respect, there is a need for large-scale studies that evaluate in detail hormone usage, frequency, form and duration.

Interestingly, in this study, the rate of serious disease was found to be lower in women with a history of leiomyoma, although it was not statistically significant. Although many studies suggest that progesterone and estrogen play key roles in the pathogenesis of leiomyomas, their functional roles have not yet been clarified [40]. We do not know whether the higher progesterone levels detected in women with leiomyoma can induce an anti-inflammatory response. The evidence to date does not support a claim that

uterine leiomyomas, which have an unclear and complex pathogenesis, protect against severe COVID-19. On the other hand, although the presence of ACE 2 has also been demonstrated in human myometrium and uterine leiomyomas, the presence of TMPRSS2 in these tissues remains unclear [41]. Therefore, the characteristics of the immune response in women with leiomyoma should be investigated in both epidemiological and molecular-based studies.

Conclusion

In conclusion, we found that some obstetric and gynecological conditions may affect the susceptibility and severity of COVID-19 in women without a history of systemic disease. Fertility problems may be more serious in women, who are more at risk. Therefore, identifying these women may be important for taking action to protect them. In the future, with larger sample sizes and better designed studies, risk factors for COVID-19 and female gender may be more clearly defined.

Limitations

This study has some limitations. First, due to the study's design, only self-reports of the participants were used. Existing gynecological histories of the participants were not subject to gynecological examination and hormone levels were not measured. Second, different virus variants may have different characteristics in terms of susceptibility and disease severity, as the timeframe in which participants contracted COVID-19 was not taken into account. Third, a larger sample size is needed to identify those factors that influence the susceptibility and severity of a disease. In addition, the study cannot be generalized as it covers women living in a particular region. On the other hand, this study may provide some degree of insight into the wider issue for future research as it is the first study to evaluate the factors affecting COVID-19 susceptibility and severity in terms of many gynecological conditions and based on women without additional systemic diseases.

Conflict of Interest Statement

The authors declare that there are no conflict of interests.

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