

# Does Endometriosis Increase Susceptibility to COVID–19 Infections? A case-control study in Women of Reproductive Age

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## Research article

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# Abstract

## Background

In today's world, coronavirus disease 2019 (COVID-19) is the most critical health problem and research is continued on studying the associated factors. But it is not clear whether endometriosis increases the risk of COVID-19.

## Methods

Women who referred to the gynecology clinic were evaluated and 507 women with endometriosis (case group) were compared with 520 women without endometriosis (control group). COVID-19 infection, symptoms, exposure, hospitalization, isolation, H1N1 infection and vaccination, and past medical history of the participants were recorded and compared between the groups using IBM SPSS Statistics for Windows version 21.

## Results

Comparison between the groups represent COVID-19 infection in 3.2% of the case group and 3% of the control group ( $P = .942$ ). The control group had a higher frequency of asymptomatic infection (95.7% vs. 94.5%;  $P < .001$ ) and fever (1.6% vs. 0%;  $P = .004$ ), while the frequency of rare symptoms was more common in the case group ( $P < .001$ ). The average disease period was 14 days in both groups ( $P = .694$ ). COVID-19 infection was correlated with close contact ( $r = .331$ ;  $P < .001$  in the case group and  $r = .244$ ;  $P < .001$  in the control group), but not with the history of thyroid disorders, H1N1 vaccination, traveling to high-risk areas, and social isolation ( $P > .05$ ).

## Conclusion

Endometriosis does not increase the susceptibility to COVID-19 infections, but alters the manifestation of the disease. The prevalence of the disease may depend on the interaction between the virus and the individual's immune system but further studies are required in this regard.

## Plain English Summary

Coronavirus disease 2019 (COVID-19 infection) is today the most critical health issue, infecting more and more people each day without vaccination or definite treatment. It is thus important to determine the risk factors of COVID-19 infection. Several diseases are considered risk factor for susceptibility to infection or higher severity of COVID-19. Endometriosis is a common benign gynecologic disease and it has been suggested that it may increase the risk of COVID-19 infections, because in both diseases immunologic pathways are involved. In the present study, 507 women with endometriosis (case group)

were compared with 520 women without endometriosis (control group) showed that endometriosis is not a risk factor for COVID-19 infection.

## Background

Coronavirus disease 2019 (COVID-19 infection), is one of the most critical pandemics ever, resulting in about a 15% mortality rate in hospitalized patients (1). As a newly emerging disease, ongoing researches are running on different aspects of the disease; yet, no vaccination or definite treatment has been found (2). The virus mainly affects the respiratory system, presenting with cough, difficult breathing, pneumonia, and in severe cases, acute respiratory distress syndrome (ARDS), need for intensive care unit (ICU) admission and mechanical ventilation (3). Some cases of COVID-19 may be complicated by multiple organ failure (MOF) which results in death (4).

Susceptibility of specific organs to COVID-19 has provoked research towards the disease mechanisms (5), which resulted in identification that the spike glycoprotein (S protein), one of the main structural components of SARS-CoV-2, facilitates binding of envelope viruses to host cells by forming homotrimers protruding on the viral surface, which attracts angiotensin-converting enzyme 2 (ACE<sub>2</sub>) (6). Therefore, SARS-CoV-2 can directly damage organs which express ACE<sub>2</sub>, including lungs, heart, kidneys and intestines (7) and the virus entry through this receptor depends on the cleavage of the S protein, which varies in different virus strains and cell types (8).

ACE<sub>2</sub> protein is also effective in the physiology and pathology of the reproductive system, including the testicles and ovaries, and fertility processes (9). COVID-19 may also affect the quality and quantity of sperm production, as well as the production of sex hormones, leading to decreased libido (10). Considering endometrial infection by SARS-CoV, it has been suggested that endometrium has a low risk of COVID-19 infection, due to the low expression of ACE<sub>2</sub> and transmembrane protease serine protease-2 (TMPRSS2), but the expression of these host receptors increase at specific stages of the menstrual cycle and varies based on the woman's age (11). Previous studies on the endometrial disease have also determined the presence of ACE<sub>2</sub> in the glandular epithelium, stroma, perivascular space, and endothelium, and its significant increase in endometrial cancer tissue (12, 13). Therefore, clinical studies are required to determine the risk of COVID-19 infection in the endometrial tissue (14).

Endometriosis is a common benign gynecologic disease, in which the endometrial tissue is implanted anywhere in the female's body outside the uterus, most commonly in the abdominal and pelvic cavities (15). The association of immune system disturbances with the incidence of endometriosis has been discovered previously (16). It has been suggested that intratracheal endometriosis may induce and/or worsen pulmonary symptoms of COVID-19 infection (17). An expert opinion has suggested specific treatment guidelines, in order to reduce the susceptibility of endometriosis patients to COVID-19 infection (18). However, to date, there is no evidence about the risk of COVID-19 infections in patients with endometriosis. Accordingly, the present study aimed to compare the risk of COVID-19 among women with or without endometriosis.

# Methods

## Study design

The included participants were asked to complete a researcher–designated checklist via email or social networks or cell phone for evaluation of Real-Time polymerase chain reaction (rt-PCR) screening test and symptoms of COVID–19, the recent history of traveling to the high-risk areas, social distancing, relationship with a patient infected with COVID–19, positive COVID–19 rt-PCR Test, isolation due to COVID–19 infection, and hospitalization due to COVID–19. History of H1N1 infection and vaccination during last year, and a positive history of medical diseases. The symptoms included fever, sore throat, nasal congestion, cough, shortness of breath, headache, weakness and muscle pain, reduced sense of smell and/or taste, ocular problems, and other (including gastrointestinal, skin, hematologic, and neuronal) complications. Patients, younger than 18 or older than 45 were excluded from the study.

This study was designed as a case-control study and conducted at Pars general hospital from May 21st to July 3rd, 2020. The study the population consisted of women with histologic confirmation of endometriosis (extracted sample during laparoscopy), compared with an age-matched control group, selected from women without endometriosis who referred to the gynecologic clinic for screening Pap smear test and had no complaints of any symptom related to endometriosis. The sample size of the study was considered at a minimum of 500 in each group, considering the estimated period prevalence of COVID–19 of 13% in the population, based on the study by Signorelli and colleagues (19), the power of the study was 80% and an alpha error of .05. The researcher selected the eligible participants according to the inclusion criteria, explained the study design and objectives to the eligible participants, and asked them to read and sign the written informed consent, and included the eligible participants (who gave consent) into the study by census method. The protocol of the present study was approved by the Ethics Committee of Pars Advanced and Minimally Invasive Medical Manners research center, Pars Hospital, Tehran, Iran. (code: 99G5018).

## Statistical analysis

For describing the categorical variables, frequency (percentage) was reported. For numeric variables, first, Kolmogorov–Smirnov test was used to assess the normal distribution of data and according to the results of this test, the numeric variables were described by mean  $\pm$  standard deviation (SD) or median and compared between the groups using independent *t-test* or Mann–Whitney U test, whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square or Fisher’s exact test. The association of variables was tested by Spearman’s correlation coefficient. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows version 21.0 (IBM Corp. 2012. Armonk, NY: IBM Corp.) was used. P values of .05 or less were considered statistically significant.

## Results

A total of 507 women were evaluated in the case group and 520 women in the control group. The mean  $\pm$  SD of the women's age was  $29.08 \pm 14.29$  in the case group and  $33.00 \pm 7.06$  in the control group ( $P = .379$ ). The majority of the case group had stage IV endometriosis ( $N = 110, 63.2\%$ ), 17.2% had stage III ( $N = 30$ ), 8% had stage II ( $N = 14$ ), 11.4% had stage I endometriosis ( $N = 20$ ). In the case group, 18.3% ( $N = 93$ ) had a positive history of infertility.

The results of comparing the COVID-19 characteristics between the case and control groups, as shown in Table 1, showed no difference between the groups in terms of COVID-19 infection ( $P = .942$ ), frequency of H1N1 vaccination, recent traveling to high-risk provinces, social distancing, close contact with an infected patient, as well as the frequency of performing screening test, admission and isolation due to COVID-19 ( $P > .05$ ); but, the frequency of symptoms ( $P < .05$ ) and H1N1 infection were significantly different between the groups ( $P < .001$ ). As shown in Table 1, the frequency of asymptomatic cases and the frequency of fever was higher in the control group ( $P < .001$  and  $.004$ , respectively), and the frequency of other symptoms was higher in the case group ( $P < .001$ ). The average disease period was 14 days in both groups ( $P = .694$ ).

Table 1

The results of comparing the coronavirus disease characteristics between the case and control groups

Variable	Categories	Case group (N = 507)		Control group (N = 520)		p-value
		Number	Percent	Number	Percent	
H1N1 infection	No	462	91.1	490	2.0	< .001*
	Yes	44	8.7	10	2.0	
H1N1 vaccine	No	488	96.3	495	97.4	.212*
	Yes	18	3.6	13	2.6	
Travel	No	470	92.7	370	69.7	.059*
	Yes	36	7.1	24	4.5	
Social distancing	No	397	78.3	267	67.8	.256*
	Yes	109	21.5	127	32.2	
Close contact	No	475	93.7	358	91.8	.979*
	Yes	31	6.1	32	8.2	
COVID-19 infection	No	490	96.6	515	97	.942*
	Yes	16	3.2	16	3	
symptoms	None	479	94.5	508	95.7	< .001*
	Fever	0	0	8	1.6	.004†
	Sore throat	7	1.4	6	1.2	.745*
	Nasal congestion	8	1.6	2	.4	.050*
	Cough	7	1.4	6	1.2	.747*
	Shortness of breath	8	1.6	6	1.2	.558*
	Headache	4	.8	3	.6	.486*
	Weakness and muscle pain	5	1.0	13	2.6	.094*
	Reduced sense of smell and/or taste	9	1.8	7	1.4	.622*
	Ocular problems	4	.8	1	.2	.179†

Results of: \*Chi square test, †: Fisher's exact test

	<b>Other</b>	11	2.2	0	0	<.001 <sup>†</sup>
<b>Screening</b>	<b>No</b>	477	94.1	476	89.6	.137*
	<b>Yes</b>	29	5.7	42	7.9	
<b>Admission</b>	<b>No</b>	505	99.6	520	100	.494 <sup>†</sup>
	<b>Yes</b>	1	.2	0	0	
<b>Isolation</b>	<b>No</b>	493	97.2	420	97.2	.790*
	<b>Yes</b>	13	2.6	12	2.8	

Results of: \*Chi square test, †: Fisher's exact test

The frequency of underlying diseases is shown in Table 2. As demonstrated in this table, 80.5% in the case group and 72.3% in the control had no underlying disease ( $P = .002$ ) and the frequency of diabetes mellitus ( $P = .038$ ), cardiovascular disease, hypertension, and lupus erythematosus were higher in the control (all  $P < .001$ ; Table 2).



Table 2

The results of comparing the frequency of underlying diseases between the study groups

	Case group (N = 507)		Control group (N = 520)		P-value
	Frequency	Percent	Frequency	Percent	
<b>None</b>	408	80.5	376	72.3	.002*
<b>Thyroid disease</b>	5	.98	3	.57	.501†
<b>Diabetes mellitus</b>	11	2.2	23	4.6	.038*
<b>Cardiovascular disease</b>	2	.4	36	7.2	< .001*
<b>Hypertension</b>	13	2.6	42	8.4	< .001*
<b>Asthma</b>	1	.2	6	1.2	.124†
<b>Allergy</b>	13	2.6	23	4.6	.057*
<b>Cancer</b>	5	1.0	11	2.2	.097*
<b>Sinusitis</b>	6	1.2	2	.4	.173†
<b>Lupus erythematosus</b>	2	.4	6	1.2	.156†
<b>Rheumatoid arthritis</b>	4	.8	26	5.2	< .001†
<b>Other</b>	18	3.6	24	4.8	.314*
Results of: *Chi-square test, †Fisher's exact test					

Studying the association of the study variables with COVID-19 infection identified close contact with a patient infected with COVID-19 as a significant risk factor, both in the case ( $r = .331$ ,  $P < .001$ ) and the control group ( $r = .244$ ,  $P < .001$ ), while other variables such as social distancing, traveling, underlying diseases, thyroid disease, and endometriosis stage were not associated with COVID-19 infection ( $P > .05$ ; Table 3).

Table 3  
The association of COVID-19 infections with the study variables in each study group

		COVID-19-positive cases in the case group (N = 16)			COVID-19-positive cases in the control group (N = 16)		
		N (%)	Pearson's coefficient	p-value	N (%)	Pearson's coefficient	p-value
<b>Underlying diseases</b>	<b>Diabetes mellitus</b>	–	.108	.611	1 (6.2%)	.202	.533
	<b>Cardiovascular disease</b>	–			1 (6.2%)		
	<b>Hypertension</b>	–			2 (12.5%)		
	<b>Asthma</b>	–			1 (6.2%)		
	<b>Allergy</b>	–			1 (6.2%)		
	<b>Rheumatoid arthritis</b>	2 (12.5%)			1 (6.2%)		
<b>Thyroid disease</b>	5 (31%)	.032	.471	3 (18.6%)	.026	.588	
<b>Admission due to COVID-19</b>	1 (6.2%)	.246	< .001	0	–	–	
<b>H1N1 vaccination</b>	1 (6.2%)	.026	.445	13 (81.2%)	.026	.554	
<b>Travel</b>	1 (6.2%)	.006	1.000	4 (25%)	.803	.465	
<b>Social distancing</b>	5 (31%)	.043	.355	4 (25%)	.089	.510	
<b>Close contact</b>	8 (50%)	.331	< .001	6 (37.5%)	.244	< .001	

## Discussion

Comparing two groups of women with and without endometriosis showed no difference in the frequency of COVID-19 infection. The prevalence of the disease depends on the interaction between the virus and the individual's immune system. Our studies' findings represent that women with endometriosis do not have a higher risk of COVID-19 and the risk of COVID-19 infection in these patients are similar to women without endometriosis who referred to the same center for routine Pap smear test. The recent COVID-19 pandemic has forced researchers to focus on the different aspects of this disease, and studying factors that can predispose the individual to disease (20). Studies have investigated the effect of nutrition (21), serum parameters, such as blood group (22) and elevated plasmin(ogen) (23), as well as

underlying autoimmune diseases, such as tuberculosis (24) and lupus erythematosus (25), on COVID-19 susceptibility. However, as far as the authors are concerned, the risk of COVID-19 infection in women with endometriosis has not been clinically evaluated, to date.

The endometrial susceptibility to COVID-19 is still under investigation. In a molecular genetic study by Henarejos-Castillo et al., analyzing data of 112 women with normal endometrial cells demonstrated that the lower expression of host proteases, related to SARS-CoV-2 infection, such as ACE<sub>2</sub> and TMPRSS2 may result in a lower risk of endometrial susceptibility to COVID-19 infection, but the expression varies in different phases of the menstrual cycle and increases during implantation and in older women (11). It is also assumed that COVID-19 can induce changes in endometrial tissue and affect the female reproductive potential (26). However, the susceptibility of endometrial tissue to COVID-19 has not been confirmed in the clinical setting (14). Studying large databases has shown that the uterine corpus endometrial carcinoma tissue is more susceptible to SARS-CoV-2 infection, which also affected the tumor prognosis after COVID-19 infection (27). Other cancer types, including gastrointestinal and urinary tract tumors have also shown higher susceptibility to COVID-19 infection, attributed to the expression of ACE<sub>2</sub> and TMPRSS2 in cancer tissues (22, 28). However, the published articles are expert opinion or molecular based and further clinical studies are required in this regard. It has been previously demonstrated that despite the indefinite pathophysiology of endometriosis, the immune system is considered as a cause of development of endometriosis and several immunologic and inflammatory changes are observed during endometriosis (29). The main immunologic changes during endometriosis include reduction of T cell reactivity, natural killer (NK) cell's cytotoxicity, increased antibody production, macrophages polarization and inflammatory mediators release (30). The increased infiltration level of immune cells, including B cell, CD4<sup>+</sup>T cell, neutrophil, and dendritic cells as well as increased expression of ACE<sub>2</sub> has been correlated with SARS-CoV-2 susceptibility in endometrial cancer (22). However, such association has not been found in endometriosis and the results of our study showed no difference in susceptibility to COVID-19 infection in endometriosis women, which maybe due to the fact that the inflammatory and immunologic pathways in endometriosis is chronic (31), while that of COVID-19 is acute.

In the current study, it was found that the frequency of COVID-19 symptoms differed between women with and without endometriosis; endometriotic women had a lower frequency of asymptomatic and febrile infection, but higher frequency of other symptoms, including gastrointestinal, dermatologic, hematologic, and neuronal disorders. These results indicated that more attention should be paid to women with endometriosis for diagnosis of COVID-19 infection, as they mainly do not present common symptoms. Of note, many of the asymptomatic cases with COVID-19 infection may be in the development period and present the symptoms in the next few days or present with uncommon symptoms that make diagnosis difficult (32). COVID-19 infection interferes with the antigen-presenting cells in the immune system and creates bilayer vesicles, which can block the expression of Pattern Recognition Receptor (PRR) and, as a result, the patient's innate immune system does not recognize them and continue to proliferate within the vesicle, they also, disable the production of Type I interferons as one

of the most important antiviral factors so it will develop as an asymptomatic disease in some cases (33). Asymptomatic COVID-19 is considered the Achilles' heel for disease control, due to the strong infectivity and transmission during this period, and the major role of asymptomatic carriers in the person-to-person disease transmission (34). As the clinical signs and computed tomography (CT), imaging do not help much in diagnosing asymptomatic carriers, the best approach to diagnose these people are rt-PCR; however, information on asymptomatic carriers is limited and the mechanism of its occurrence needs further investigation (35). We supposed that the different frequency of asymptomatic COVID-19, lower frequency of fever, and higher frequency of uncommon symptoms in women with endometriosis in the present study can be attributed to the immune interactions during endometriosis (15). It has been previously suggested that patients with immune-mediated inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease have different disease characteristics of COVID-19 (36). The immune system should fight against SARS-CoV-2 by activation of cellular and innate inflammatory responses (37), which may be altered by the underlying immune dysfunction in the patient (38) and hence cause the different response of women with endometriosis to COVID-19, as shown in the present study. Further molecular studies are required to understand the exact mechanism of this finding. Another important factor affecting COVID-19 disease course is the underlying disease in the patient (39). In our study, the majority of women with endometriosis had no concomitant disease and the frequency of underlying diseases, such as cardiovascular diseases, hypertension, and lupus erythematosus were higher in the control group, which can be another cause for the different symptoms of the two study groups.

We also analyzed factors associated with COVID-19 infection and the results revealed that close contact with a patient infected with COVID-19 was the only risk factor in both groups that resulted in a slightly increased chance (.3- and .2-folds higher odds in the case and control groups, respectively), while other variables such as social distancing, traveling, underlying diseases, thyroid disorders, and endometriosis stage were not associated with COVID-19 infection. As far as no vaccination and definite treatment are available for COVID-19, preventive measures should be considered by everyone to reduce the transmission rate and the prevalence of this epidemic (40). Accordingly, several guidelines have been devised for flattening the curve of COVID-19 (41). As the results of our study showed, close contact with an infected patient was the most important factor for both groups, which indicate the need for increasing the knowledge and awareness of the general population about the necessary precautions to be taken during the current outbreak (42).

The limitations of the present study include the cross-sectional nature of the study and lack of follow-up. Therefore, we could only suggest associations, rather than the causal relationship between the study variables. Furthermore, we matched the control group in terms of age with the case group and selected women were from the same medical center; however, differences in other characteristics between the groups may affect the results. Also, we recruited participants by census method and the nonrandomized patient selection increases the chance of confounders on the results.

# Conclusions

The results of the present study showed that endometriosis does not increase the susceptibility to COVID-19 infection, but changes the presenting symptoms. Therefore, more attention should be paid for accurate diagnosis of COVID-19 in women with endometriosis. The lower rate of fever and higher rate of uncommon symptoms in women with endometriosis may be due to the immune interactions of these two diseases. Since the exact mechanism of infection with this virus is not fully understood and no specific drug or vaccine has been designed for it so far, the most important task at present is to eliminate the transmission cycle. Identifying the predisposing factors can help diagnose the high-risk patients and achieve this aim.

# Abbreviations

- COVID-19 infection: Coronavirus disease 2019
- ARDS: acute respiratory distress syndrome
- ICU: intensive care unit
- MOF: multiple organ failure
- ACE<sub>2</sub>: angiotensin-converting enzyme 2
- TMPRSS2: transmembrane protease serine protease-2
- rt-PCR: Real-Time polymerase chain reaction
- SD: standard deviation
- NK: natural killer
- PRR: Pattern Recognition Receptor
- CT: computed tomography

# Declarations

- **Ethics approval and consent to participate:** Written informed was obtained from the participants.
- **Consent for publication:** All participants gave consent for anonymous publication of their results.
- **Availability of data and materials:** Available upon request.
- **Competing interests:** The authors of the present study declare that they have no competing interests.
- **Funding:** This study is supported by, Pars General hospital, Tehran, Iran. The funder had role in data collection, but had no role in decision to publish, or preparation of the manuscript.
- **Authors' contributions:** Study concept and design: SC and BM, drafting of the manuscript FJ and MA and DS and critical revision of the manuscript: SC, and ZSM Statistical Analysis: MAP and FK. All of the authors have given final approval of the version to be published.
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