Received: 16 February 2022 | Revised: 12 July 2022 | Accepted: 18 July 2022

DOI: 10.1111/aji.13602

AJRI American Journal of Reproductive Immunology WILEY

ORIGINAL ARTICLE

COVID-19 susceptibility in endometriosis patients: A case control study

Marta Barretta | Federica Savasta | Giuliana Pietropaolo | Allegra Barbasetti | Valeria Barbera | Michele Vignali

Department of Biomedical Science for the Health, University of Milan, Milan, Italy

Correspondence
Marta Barretta, Department of Biomedical Science for the Health, University of Milan, Macedonio Melloni Hospital, via Macedonio Melloni 52, 20129 Milan, Italy.
Email: m.barretta2112@gmail.com

Abstract

Problem: Starting from November 2019, the world has had to face a devastating pandemic caused by SARS-CoV-2. Various studies have identified potential risk factors facilitating the infection, however it has not been demonstrated whether endometriosis might represent one of them.

The purpose of this study was to evaluate if patients with endometriosis had a higher risk of contracting COVID-19 infection and, in such case, whether they developed a more severe infection than the general population. Furthermore, this study evaluated the possible correlation with the stage of endometriosis, based on the r-ASRM score, and the potential worsening of the disease during the SARS-CoV-2 infection.

Method of study: A case-control study was conducted from March 2020 to April 2021 at Macedonio Melloni Hospital, in Milan. A total of 401 women were recruited. The cases were 201 women with clinical or surgical diagnosis of endometriosis. The control group consisted of 200 women, without the disease. All women completed a self-administered questionnaire which evaluated their demographic and clinical characteristics, as well as a potential diagnosis of Covid-19.

Results: Comparison between the two groups showed that women with endometriosis had a higher frequency of COVID-19 than the control subjects (23% vs. 13.5%, $P = .014$), with a greater prevalence of fever (14.4% vs. 6%, $P = .008$) and myalgias or arthralgias (11.4% vs. 4.5%, $P = .01$).

In multivariable logistic regression analyses, women with endometriosis had a higher risk of contracting SARS-CoV-2 infection (OR = 2.11, 95% IC: 1.20–3.80), regardless the stage of the disease.

Conclusion: Endometriosis increases the susceptibility to COVID-19, and women who suffer from it should be considered as fragile patients, worthy of prior access to SARS-CoV-2 vaccination campaign.

KEYWORDS
coronavirus, COVID-19 susceptibility, endometriosis, hyperinflammatory diseases, immunologic factors, risk factors, SARS-CoV-2

1 | INTRODUCTION

Starting from November 2019, a pandemic caused by a respiratory virus, subsequently named SARS-CoV-2, started to spread worldwide.[1] In a short time, all sanitary facilities had to reorganize their activities and priorities in order to provide healthcare to these patients, often found in critic conditions. Specifically, many surgeries dedicated to chronic diseases' follow up were suspended or reduced, including those regarding patients with endometriosis.[2]

Endometriosis is a common benign disease characterized by a chronic inflammatory state which causes severe pelvic pain and infertility.[3–6] Almost 10% of women in fertile age suffer from this condition and, given its chronicity, it requires periodic check-ups in dedicated clinics, specific instrumental exams, complex surgeries and it can often call for treatments in ART centers.[7–9]

The physiopathology of Endometriosis is complex and an important role is played by the dysregulation of the immune system, which enables the development and sustainment of the disease.[10–13]

High levels of angiogenic factors and inflammatory cytokines have been found in the peritoneal fluid of affected patients, including IL-1β, IL-6, IL-10, which, in turn, stimulate the production of VEGF (vascular endothelial growth factor) and MCP-1 (monocyte chemotactic protein) by macrophages. This generates a pro-inflammatory state characterized by the activation of macrophages and neutrophils, and a reduction in the activity of natural killer lymphocyte.[14]

Similarly, SARS-CoV-2 infection is also associated with an uncontrolled immune response, commonly referred to as "cytokine storm," which is characterized by an increase in the circulating levels of proinflammatory cytokines, such as IL-1β, IL -6, and of chemokines such as CXCL10 and CCL2.[15–19]

In light of the immunological similarities between COVID-19 and hyperinflammatory diseases,[20–22] it is plausible to hypothesize that there could be a positive correlation between SARS-COV-2 infection and endometriosis.

To date, the literature examining this potential correlation is scarce. Some studies suggest a possible higher susceptibility in patients with thoracic endometriosis,[23] and only one study by Moazzami et al.[24] investigated the correlation between Covid-19 and endometriosis. In their study, however, Moazzami et al. did not highlight any difference in susceptibility to COVID-19 disease in women with endometriosis, probably because of the limited observation period of the study and the lack of follow-up.

The present study was conducted in the Italian Pandemic context between March 2020 and April 2021, when the number of positives and the number of vaccinated were 6 million and 2 million, respectively. The objective of this study is to evaluate if patients with endometriosis may be more susceptible to COVID-19 infection than the general population, and, subsequently, if they develop more severe symptoms.

This study also aims to evaluate a possible correlation between the stage of endometriosis, based on the r-ASRM classification, and COVID-19 disease.

2 | MATERIALS AND METHODS

A case control study was conducted in Macedonio Melloni Hospital, in Milan, to evaluate the correlation between endometriosis and COVID-19.

Four hundred and fifty women referring to our hospital's pelvic pain clinic in the period between 2020 and 2021 were recruited. The women were aged between 18 and 50 years, suffering from pelvic pain or infertility associated to suspected endometriosis.

Of the 450 potential cases, 148 were ineligible for the study due to the absence of endometriosis and 101 were excluded as they were untraceable and could not answer the questionnaire. Of the remaining 201, 89 patients were diagnosed with endometriosis after surgery (with a histological confirmation). For the other 112 cases, the diagnosis was made after an accurate clinical-instrumental evaluation carried out by competent physician specialized in the study and management of this disease. The study population was subsequently divided into four stages, from I to IV, according to the ASRM classification[25] and depending on the stage of development of the disease. The group included both operated and non-operated patients and it leveraged the high predictivity of ultrasound in defining the stage of the disease,[26–29] as the literature corroborates.

The control group was recruited by selecting patients of the same age who referred to our gynecologic clinics from January to April 2021. This group of patients did not complain painful symptoms related to endometriosis,[30] had no clinical or ultrasound signs of disease, and had no previous histological diagnosis of endometriotic disease.[28] For patients who underwent surgery, reports of the interventions and the related histological examinations were analyzed in order to exclude any patients with endometriosis: eight patients were excluded from this group and reinserted into the group of cases, thus obtaining a total of 200 patients.

On the basis of the initial hypothesis that led the present study, a detailed questionnaire (Figure 1) was developed and administered to the patients of both groups, subject to their verbal consent.

Prior to drawing up the questionnaire, a thorough analysis of the literature[31–32] was carried out in order to verify if there was already a content that would enable us to evaluate the characteristics of the patients and the diseases under study. Subsequently, we defined the

Sistema Socio Sanitario
OSPEDALE FATEBENEFRATELLI E OFTALMICO
OSPEDALE MACEDONIO MELLONI
Regione Lombardia
ASST FATEBENEFRATELLI SACCO

UNIVERSITA' DEGLI STUDI DI MILANO
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Michele Vignali

Dear Madam,

we would like to ask you to take two minutes to evaluate the epidemiological trend of SARS-CoV-2 infection in the female population.

A-PERSONAL HISTORY
Comorbidities:
Age
Smoking YES - NO
Weight/height
Do you suffer from any pathology? (Moderate/severe allergic asthma; Other chronic lung diseases (fibrosis, sarcoidosis, TB, COPD, emphysema); Diabetes mellitus; Hypertension; Ischemic heart disease; Chronic renal failure; Autoimmune diseases).
Do you take chronic medical therapies that compromise your immune system? (e.g. cortisone, immunosuppressants)
Have you ever been diagnosed with a tumor? If so, which one?

B-COVID MEDICAL HISTORY

Have you had the SARS-CoV-2 infection in the last year? (diagnosis established by positive nasopharyngeal swab)
If yes, for how many days was the swab positive?
Have you had a cough?
Fever?
Myalgia and arthralgia?
Headache?
Sore throat? Runny nose?
Diarrhea?
Nausea or vomiting?
Loss of taste or smell?
Difficulty breathing?
Pneumonia? If so, were you hospitalized? For how many days?
Did you have any respiratory complications? (Did you receive any breathing aids? Which ones? oxygen mask, CPAP, oro-tracheal intubation)?
Did you have any cardiovascular complications or sequelae?
Did you have thromboembolic complications?
Have you had any neurological complications or sequelae?

In the last year, have you had any symptoms suspicious of Sars-Cov2 infection? (But not diagnosed by swab: specify if swab negative or not performed)
Fever?
Respiratory symptoms?
Headache?
Gastrointestinal symptoms?
Loss of taste or smell?

4) Have you been vaccinated against the Sars-Cov2 virus? If so, when? With what vaccine?
Have you been in close contact with a positive person?
Have you been placed in quarantine?

C-EVALUATION OF ENDOMETRIOSIS SYMPTOMS:
During the period of infection and upon resolution of the infection did you notice a worsening of your endometriosis-related symptoms? How would you describe this on a scale of one to ten?
If you are undergoing medical therapy for endometriosis, were you able to take your therapy regularly during COVID-19?
Did you have a post-COVID gynecological check-up? Has the clinical picture remained stable or changed?
The diagnosis of ovarian/peritoneal/profundal/pulmonary endometriosis has been confirmed?

FIGURE 1 Questionnaire submitted to patients

formulation methods of each question.[33] The resulting questionnaire was validated by a group of four experts, two gynecologists from the center for the treatment of pelvic pain and endometriosis, one anesthetist and one infectious disease specialist, employed in specialized canters for the management of COVID-19 (located at Sacco Hospital Milan and Vizzolo Predabissi Melegnano Hospital, respectively).

A prototype of the questionnaire was administered to a group of 30 residents in the Gynecology and Obstetrics unit (selected with the same criteria as the participants in the final validation), who evaluated all questions. In this phase, the participants' opinions on the relevance, comprehensibility, and construct validity of the questions were collected, complementing the questionnaire data. During the review of the questionnaire, the question "did you develop chronic pelvic pain after Covid-19 infection?" was removed because the observation period would not be long enough from the time of infection to the onset of symptoms to allow definition of the pelvic pain as "chronic." Furthermore, questions were rearranged by dividing the questionnaire into three parts. The first part (Part-A. Medical History) collected data relating to age, BMI, cigarette smoking habits, as well as the presence of medical diseases considered as risk factors for SARS-CoV-2 infection, including pregnancy. The second part (Part B-COVID-19 disease) evaluated the development of COVID-19 disease in the period between March 2020 and April 2021, its clinical manifestations and complications. The third part (Part C-Evaluation of endometriosis symptoms) investigated if patients had noticed a worsening of endometriosis-related symptoms during and after COVID-19 infection and invited them to rate the severity of symptoms on a scale of 1–10.

Patients under the age of 18 and over 50 were excluded, as well as pregnant patients in the study period. BMI (kg/m2) was calculated based on the weight and height of each patient, measured at the time of data collection. The clinical history of the patients was investigated by assessing in detail whether they had moderate/severe allergic asthma, other chronic lung diseases (fibrosis, sarcoidosis, TB, COPD, emphysema), diabetes mellitus, hypertension, ischemic heart disease, chronic renal failure, autoimmune disease, cancer or use of chronic medical therapies that could compromise the functioning of the immune system.

Patients were considered affected by COVID-19 only with a positive result to the nasopharyngeal molecular swab, documented by the patients themselves or viewed from the electronic health record. In case of confirmed infection, the following symptoms were investigated[34]: cough, fever (T > 37.5°C), myalgia and arthralgia, headache, pharyngodynia, rhinorrhea, diarrhea, nausea or vomiting, loss of taste or smell and difficulty respiratory. The development of respiratory, cardiovascular, thromboembolic and neurological complications or sequelae was also investigated. The patients were asked if they had been vaccinated against SARS-CoV-2, so as to include in the statistical analysis only positive patients in the period prior the date of the vaccine.

Data were analyzed using R Core Team (2021) software. A: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Numerical variables were described by mean ± standard deviation (SD), and were compared by Student *t*-test for independent samples.

For categorical variables, the frequency (in percentage) was reported, and the differences in the case and control groups were evaluated using the chi-square (χ^2) test with Yates correction or the test Fisher's exact.

The strength of association between the variables was calculated using the odds ratio (OR), considering a 95% confidence interval (CI). The results obtained with the univariate analysis were further analyzed through multivariate analysis by logistic regression.

The values of *P*-value (P) were considered statistically significant if lower than or equal to .05.

3 | RESULTS

The mean ± SD of the patient's age in the case group was 41.55 ± 6.59, whilst for the control group was 38.1 ± 9.81.

The majority of patients with endometriosis had an advanced stage of disease: 37.8% ($N = 76$) had a stage IV disease and 39.3% ($N = 79$) had a stage III. For the remaining patients, 10.9% ($N = 22$) presented a stage II disease and 11.9% ($N = 24$) a stage I disease.

The clinical characteristics of the recruited women, divided into the two study groups, are shown in Table 1. Obesity (BMI ≥ 30) was found in 20 (9.9%) patients in the case group and in 18 (9.5%) in the control group. Smokers in the case group were 28 (13.9%) compared with 56 (28%) in the control group.

Comorbidities were scarcely represented in both groups: the asthmatic pathology was present in 10 (5%) patients in the case group and in 13 (6.5%) in the control group; chronic lung diseases were underrepresented in both groups, affecting 2 (1%) patients in the case group and 0 patients in the control group. Type 2 diabetes mellitus was present in 3 (1.5%) patients in the case group and in 1 (.5%) in the control group. No patient had chronic renal failure. An autoimmune disease was diagnosed in 7 (3.5%) patients in the case group and in 11 (5.5%) in the control group. Both, immunosuppression and the presence of cancer were poorly represented in both groups, with respectively 2 (1%) and 1 (.5%) affected patients in the case group, and 1 (.5%) and 1 (.5%) in the case group.

No statistically significant differences were obtained in the two study groups, except for hypertension and smoking, which presented instead a statistically significant difference in the two study groups, being more represented in the control group ($P = .0002$ and $P = .0005$, respectively).

The differences in terms of frequency of SARS-CoV-2 infection and associated symptoms in the two study groups are shown in Table 2.

The difference in the number of COVID-19-infected patients in the endometriosis group compared with the control group was statistically significant, with a total of 46 (23%) patients in the case group compared to 27 (13.5%) in the control group ($P = .014$).

Fever and myalgias and/or arthralgias were proportionally more frequent in the group of patients with endometriosis, with a statistically significant difference compared with the control group ($P = .008$ and

TABLE 1 Clinical characteristics in the case and control groups

	Endometriosis					
	Yes		No			
Variable	*n*	(%)	*n*	(%)	*P*-value	Test
Obesity						
No	181	(90.1)	182	(90.5)	0,74	Chi squared
Yes	20	(9.9)	18	(9.5)		
Smoking						
No	173	(86.1)	144	(72)	0,005	Chi squared
Yes	28	(13.9)	56	(28)		
Asthma						
No	191	(95)	187	(93.5)	0,51	Chi squared
Yes	10	(5)	13	(6.5)		
COPD						
No	199	(99)	200	(100)	0,49	Fisher's exact test
Yes	2	(1)	0	(0)		
Type 2 diabetes						
No	198	(98.5)	199	(99.5)	0,62	Fisher's exact test
Yes	3	(1.5)	1	(.5)		
Hypertension						
No	185	(92)	199	(99.5)	0,0002	Fisher's exact test
Yes	16	(8)	1	(.5)		
Cardiovascular diseases						
No	199	(99)	200	(100)	0,49	Fisher's exact test
Yes	2	(1)	0	(0)		
Chronic renal failure						
No	201	(100)	200	(100)	1	Fisher's exact test
Yes	0	(0)	0	(0)		
Autoimmune diseases						
No	194	(96.5)	189	(94.5)	0,32	Chi squared
Yes	7	(3.5)	11	(5.5)		
Immuno-suppression						
No	199	(99)	199	(99.5)	1	Fisher's exact test
Yes	2	(1)	1	(.5)		
Cancer						
No	200	(99.5)	199	(99.5)	1	Fisher's exact test
Yes	1	(.5)	1	(.5)		

$P = .01$, respectively). The remaining symptoms were reported similarly by patients of both groups, and none of them developed important complications or sequelae.

Table 3 shows the distribution of cases and controls according to age, obesity, smoking, endometriosis classified into stages I to IV, and other comorbidities with raw and adjusted ORs. The age of the patients was divided into three groups: <36 years, 36–44 years, 45 years; obesity was considered for BMI ≥ 30; other comorbidities were the pathologies considered in Table 1, which in the statistical analysis were evaluated as a single composite variable, since they were underrepresented in the total sample of patients.

The results obtained from the univariate analysis showed that there was no association between COVID-19 disease and age (OR = 1.21, 95% CI: .65–2.26), obesity (OR = 1.02, 95% CI: .40–2.28), smoking (OR = 1. 30, 95% CI: .70–2.32) or other comorbidities (OR = 1.02, 95% CI: .49–2.07). As for the risk of infection in patients with endometriosis, an OR of 1.9 (95% CI: 1.14–3.24) was obtained.

TABLE 2 Comparison of symptoms of SARS-CoV-2 infection

	Endometriosis					
	Yes		No			
Variable	*n*	(%)	*n*	(%)	*P*-value	Test
COVID-19						
No	155	(77)	173	(86.5)	.014	Chi squared
Yes	46	(23)	27	(13.5)		
Fever						
No	172	(85.6)	188	(94)	.008	Chi squared
Yes	29	(14.4)	12	(6)		
Cough						
No	191	(95)	197	(98.5)	.08	Fisher's exact test
Yes	10	(5)	3	(1.5)		
Dyspnea						
No	191	(95)	190	(95)	1	Fisher's exact test
Yes	10	(5)	10	(5)		
Anosmia/ageusia						
No	176	(87.6)	185	(92.5)	.09	Chi squared
Yes	25	(12.6)	15	(7.5)		
Pharyngodynia/rhinorrhea						
No	188	(93.5)	191	(95.5)	.32	Chi squared
Yes	13	(6.5)	9	(4.5)		
Myalgia/arthralgia						
No	179	(88.6)	191	(95.5)	.01	Chi squared
Yes	23	(11.4)	9	(4.5)		
Headache						
No	180	(89.5)	189	(94.5)	.06	Chi squared
Yes	21	(10.5)	11	(5.5)		
Nausea/vomit						
No	194	(96.5)	196	(98)	.54	Fisher's exact test
Yes	7	(3.5)	4	(2)		
Diarrhea						
No	192	(95.5)	195	(97.5)	.41	Fisher's exact test
Yes	9	(4.5)	5	(2.5)		
Chest pain						
No	197	(98)	200	(100)	.12	Fisher's exact test
Yes	4	(2)	0	(0)		
Neumonia						
No	199	(99)	200	(100)	.49	Fisher's exact test
Yes	2	(1)	0	(0)		

Similarly, results obtained from multivariate analysis confirmed that age, smoking, obesity, and other comorbidities are not associated with COVID-19, whereas endometriosis presented an adjusted OR of 2.11 (95% CI: 1.20–3.80), thus confirming the presence of a significant statistical association

4 | DISCUSSION

Several studies have shown that the pandemic has contributed to a worsening of the quality of life in patients with endometriosis[35–38]; however, there is a lack of reliable data on whether or not patients with

TABLE 3 Distribution of cases and controls based on selected variables and estimates of raw and adjusted odds ratios (ORs) relative to 95% confidence intervals (95% CI)

	COVID-19					
	Yes		No			
Variable	*n*	(%)	*n*	(%)	Raw OR (IC 95%)	Adjusted OR (IC 95%)
Age						
<36 years	23	(33.8)	106	(34.1)	Ref.	Ref.
36-44 years	18	(26.5)	102	(32.8)	.81 (.41-1.59)	.68 (.32-1.39)
≥45 years	27	(39.7)	103	(33.1)	1.21 (.65-2.26)	1.08 (.57-2.08)
Obesity						
No	66	(90.4)	297	(90.5)	Ref.	Ref.
Yes	7	(9.6)	31	(9.5)	1.02 (.40-2.28)	1.11 (.42-2.58)
Smoking						
No	55	(75.3)	262	(79.9)	Ref.	Ref.
Yes	18	(24.7)	66	(2.1)	1.30 (.70-2.32)	1.65 (.86-3.07)
Endometriosis						
No	27	(37.0)	173	(52.7)	Ref.	Ref.
Yes	46	(63.0)	155	(47.3)	1.90 (1.14-3.24)	2.11 (1.20-3.80)
I	5	(6.8)	19	(5.8)	1.64 (.51-4.46)	–
II	7	(9.6)	15	(4.6)	2.66 (.88-7.26)	–
III	19	(26.0)	60	(18.3)	1.97 (1.01-3.76)	–
IV	15	(20.5)	61	(18.6)	1.53 (.75-3.02)	–
Other comorbidities						
No	61	(83.6)	275	(83.8)	Ref.	Ref.
Yes	12	(16.4)	53	(16.2)	1.02 (.49-1.97)	1.02 (.47-2.07)

endometriosis have an increased risk of developing COVID-19 disease or if they experience a more severe infection.

The study conducted by Moazzami et al.[24] evaluated the risk of acquiring COVID-19 disease in 507 women with endometriosis versus 520 without endometriosis attending the Tehran hospital from May to July 2020. This study highlighted that SARS-CoV-2 infection rates among the two groups of women were of 3.2% and 3%, respectively, with no statistically significant difference between them. The authors believe that further investigations are needed to explain the lack of evidence on the increased susceptibility to such infections in patients with endometriosis.

In addition, some authors consider rare forms of thoracic endometriosis as a risk factor for COVID-19 disease. Be that as it may, the rarity of this form of endometriosis and the related literature does not present sufficient evidence.[39–40]

According to our results, endometriosis can be considered as a risk factor for COVID-19 infection, since twice as many patients in the case group have developed the infection compared to the control group. This association does not depend on pre-existing clinical conditions, nor on the severity of endometriosis measure with r-ASRM score. Endometriosis does not affect the severity of SARS-CoV-2 disease, although patients with endometriosis presented a higher frequency of fever and myalgias or arthralgias.

Regarding clinical manifestations and the severity of the disease, Moazzami et al., showed a lower frequency of asymptomatic infection and fever in patients with endometriosis, as well as a higher frequency of additional symptoms, such as gastrointestinal, dermatological, hematological or neurological manifestations. These results were correlated with the baseline conditions of the patients in the control group.

Conversely, in the present study, fever and myalgias or arthralgias were significantly more prevalent in patients with endometriosis compared to the control group, whereas no differences were found for the other symptoms investigated.

This partial discordance of results could be due to the different size of the sample examined; in fact, our data refers to a sample of 46 positive women out of 201 patients investigated (23%), whereas the Iranian study, considers only 16 positive women out of 507 (3.1%).

In addition, in assessing the ORs of the study population, a statistically significant association was observed, only between COVID-19 and endometriosis, whereas no association was found for age, smoking, obesity, and other comorbidities. This finding is apparently at odds with what is known in literature, namely that smoking and obesity are risk factors for SARS-CoV-2 infection, as is older age.[41–46] A possible explanation to the discrepancy lies in the relative low average age of the study sample, which is forced by the endometriotic disease, as well

as by the poor representation of the above mentioned risk factors in the study population (only 23% smokers and 9% obese, for instance).

The main hypothesis of the present study is based on the immunological dysregulation that characterizes both, endometriosis and COVID-19.

The transtubal theory, first suggested by Sampson,[47] claims that menstrual blood containing fragments of endometrium, after traveling retrograde through the fallopian tubes, implants on the peritoneal surface of abdominopelvic organs and tissues. With subsequent menstrual cycles, such ectopic tissue would undergo a process of proliferation and bleeding similar to that of intrauterine endometrium, resulting in the formation of endometriotic implants. Retrograde menstruation is seen in approximately 80%–90% of women, but only about 10% of these women have endometriosis.[48,49] This difference in percentage indicates that endometriotic pathology involves the ability of cell populations refluxed with retrograde menstruation to establish molecular mechanisms of adhesion to the peritoneum, proliferation, invasion of the extracellular matrix, vascularization, and even evasion from a local immunosurveillance system.[50–53]

Numerous aspects of the immune system are altered in endometriosis, including inhibited T-cell-mediated cytotoxicity to endometrial cells, diminished natural killer (NK) cell activity and increased numbers of activated macrophages and proinflammatory cytokines.

In particular, NK cells might be less effective in killing autologous dendritic cells loaded with endometrial self-antigens, thus facilitating their presentation to autoreactive T cells and consequent production of autoantibodies.[54] Indeed, it has been observed that the humoral immune response is enhanced in patients with endometriosis, resulting in an increased B lymphocyte cell and autoantibody production. Immunohistochemical and gene expression microarray analysis revealed that abundant amounts of plasma cells and activated macrophages were found in endometriotic lesions, with highly expressed cytokine B lymphocyte stimulator (BLyS).[55] This resulted in a remarkable production of autoantibodies such as antiendometrial, anti-DNA, antiphospholipid, and antinuclear antibodies.[56]

As a matter of fact, there is a strong association between endometriosis and autoimmunity, demonstrable by the higher prevalence of autoimmune diseases in women affected by endometriosis such as systemic lupus erythematosus, celiac disease, inflammatory bowel disease and autoimmune thyroiditis.[57]

Hence, endometriosis is characterized by the existence of autoantibodies and perpetuated inflammatory reactions caused by the loss of immune tolerance and by the dysfunction of the immune system. The key component of this "dysfunctional system" are the macrophages, which are differentiated into pro-inflammatory (classical/M1) or anti-inflammatory (alternative/M2) phenotypes depending on the peritoneal environment: The number of both types of macrophages increases in endometriosis regardless of the stage of the disease. At the early stages, M1 macrophages are further differentiated by inflammatory activity.[58] They exhibit decreased phagocytic capacity and increased activation of NF-B pathways leading to the downstream upregulation of pro-inflammatory cytokines (TNF-α, proIL-1β, and IL-6) growth factors and adhesion molecules.[59] At advanced stage, M2 macrophages are the dominant phenotype. They promotes endometriosis progression by angiogenesis, neurogenesis, and invasion, resulting in organ damage and malfunction.[58–60]

These immune-mediated mechanisms are also involved in COVID-19 physiopathology.

SARS-CoV-2 is an RNA virus that is able to infect cells of the human body, particularly the respiratory system, through the surface spike protein.[61,62] This protein is recognized by the cells of the immune system to prevent and counteract the invasion by the virus. Macrophages and NK cells play a key role in the defense against viruses.[63] These cellular elements capable of recognizing virus-infected cells and eliminating them through processes of apoptosis and cytotoxicity are precisely those altered in patients with endometriosis. The reduced functioning of these cells, just as it is not able to remove endometriotic implants from peritoneal surfaces, might not be able to recognize and eliminate cells infected by SARS-CoV-2 virus, justifying the increased risk of COVID-19 observed in these patients.

In the control of SARS-CoV-2 infection, another important role is played by T cell immunity. Antigen-specific CD4 and CD8 T cells and neutralizing antibody responses play protective roles against SARS-CoV-2, while impaired adaptive immune responses, as in endometriosis, may lead to poor disease outcomes.[64]

In fact, T cell subset profiles are altered in women with endometriosis.[59] Cytokine secretion by T helper (TH) cells is shifted toward TH2, which is involved in the suppression of cell-mediated immunity, potentially leading to poor immunosurveillance.[65] There are also higher numbers of TH17 cells in the peritoneal fluid of endometriosis patients, and consequently higher concentrations of IL-17, which stimulates production of cytokines that induce angiogenesis and inflammation.[66]

Similar to endometriosis, activation and infiltration of immune cells are entailed in the pathogenesis of organ injury in patients with COVID-19. Pro-inflammatory cytokines and chemokines, including interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10 and CCL2, are significantly increased in Covid-19 patients and the expression levels of some of these cytokines, such as IL-1, IL-6, IL-10, and IL-18, have been demonstrated to be associated with disease severity.[67–69] In this condition, activated macrophages will produce excessive proinflammatory cytokines, polarize into the inflammatory M1 phenotype and exhibit cytotoxic dysfunction. Excessive production and release of pro-inflammatory cytokines and chemokines can cause severe organ damage in critical cases.

In conclusion, there are similarities in the immune response in both disease conditions, and organ damage in COVID-19 appears to be largely immune-mediated, similar to endometriosis and, even more, to autoimmune diseases.[70] In fact, the SARS-CoV-2 virus can disturb self-tolerance of host antigens and the development of some antibody, such as antinuclear antibodies (ANA), anti- cytoplasmic neutrophil antibodies (ANCA) and antiphospholipid (APL) has been observed in COVID-19.[71]

Based on these principles, the aim of our study was not only to evaluate if patients with endometriosis may be more susceptible to COVID-19 infection than the general population, but also whether

endometriosis, depending on its stage, could influence the severity of the disease.

Whilst our results showed that endometriosis patients had an increased susceptibility to contract COVID-19, possibly due to the poor immuno-surveillance, they did not have a more severe course of the infection, which we would have expected, given the significant inflammatory state that characterizes patients with endometriosis.

The low significance of this result could be due to certain limitations of this study.

Firstly, a potential selection bias has to be considered, since all the patients enrolled came from Macedonio Melloni Hospital, in Milan. Secondly, the sample size has to be increased in order to corroborate our findings. Furthermore, we did not find a significant correlation between the severity of endometriosis and the risk of contracting COVID-19 infection, which we would have expected, considering the differences of the immune system depending on the stage of endometriosis.

We believe that the modest representativeness of our sample, stratified in single stages, could justifies our results. Moreover, another possible reason could depend on the classification system used to stratify the patients. In fact, the r-ASRM classification, which is the most used in clinical practice, does not entail a correlation between the severity of the disease and the prognosis and clinical outcome of the patients. For this reason, future research using a different classification system, for example the #ENZIAN score,[72–74] which evaluates more in detail the presence of deep endometriosis, might lead to the expected results.

5 | CONCLUSIONS

Our study shows that patients with endometriosis have an increased risk for SARS-CoV-2-induced infection (OR = 2.11, 95% CI: 1.20-3.80). This association did not depend on pre-existing clinical conditions or on the severity of endometriosis.

In light of our results, we believe that this study presents important practical implications. In the current pandemic context where there are still people who are skeptical about the efficacy and safety of vaccines, we believe it is crucial to properly inform these women about the benefits of vaccination. This is especially important given the fact that the affected population are patients of childbearing age, in whom a possible pregnancy could pose complications both in relation to the underlying endometriosis and to the possible SARS-CoV-2 infection.

CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Marta Barretta https://orcid.org/0000-0002-9045-9397

REFERENCES

1. Chams N, Chams S, Badran R, et al. COVID-19: a multidisciplinary review. *Front Public Health*. 2020;8:383.
2. Evans S, Dowding C, Druitt M, Mikocka-Walus A. "I'm in iso all the time anyway": a mixed methods study on the impact of COVID-19 on women with endometriosis. *J Psychosom Res*. 2021;146:110508.
3. Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. *Nat Rev Endocrinol*. 2014;10:261.
4. Greene AD, Lang SA, Kendziorski JA, Sroga-Rios JM, Herzog TJ, Burns KA. Endometriosis: where are we and where are we going?. *Reproduction*. 2016;152(3):R63-R78.
5. Giudice LC, Kao LC. Endometriosis. *Lancet*. 2004;364(9447):1789-1799.
6. Leyland N, Casper R, Laberge P, Singh SS, SOGC. Endometriosis: diagnosis and management. *J Obstet Gynaecol Can*. 2010;32(2):S1-S32.
7. Viganò P, Parazzini F, Somigliana E, Vercellini P. Endometriosis: epidemiology and aetiological factors. *Best Pract Res Clin Obstet Gynaecol*. 2004;18(2):177-200.
8. Dunselman GA, Vermeulen N, Becker C, et al. European Society of Human Reproduction and Embryology ESHRE guideline: management of women with endometriosis. *Hum Reprod*. 2014;29(3):400-412.
9. Bulletti C, Coccia ME, Battistoni S, Borini A. Endometriosis and infertility. *J Assist Reprod Genet*. 2010;27(8):441-447.
10. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. *Fertil Steril*. 2012;98(3):511-519.
11. Ahn SH, Monsanto SP, Miller C, Singh SS, Thomas R, Tayade C. Pathophysiology and immune dysfunction in endometriosis. *Biomed Res Int*. 2015;2015:795976.
12. Symons LK, Miller JE, Kay VR, et al. The immunopathophysiology of endometriosis. *Trends Mol Med*;24(9):748-762.
13. Zhang T, De Carolis C, Man GCW, Wang CC. The link between immunity, autoimmunity and endometriosis: a literature update. *Autoimmun Rev*. 2018;17(10):945-955.
14. Oosterlynck DJ, Cornillie FJ, Waer M, Vandeputte M, Koninckx PR. Women with endometriosis show a defect in natural killer activity resulting in a decreased cytotoxicity to autologous endometrium. *Fertil Steril*. 1991;56:45-51.
15. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev*. 2020;53:25-32.
16. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. *J Med Virol*. 2021;93(1):250-256.
17. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol*. 2020;39(7):2085-2094.
18. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; What we know so far. *Front Immunol*. 2020;11:1446.
19. Kim JS, Lee JY, Yang JW, et al. Immunopathogenesis and treatment of cytokine storm in COVID-19. *Theranostics*. 2021;11:316-329.
20. Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. *Nat Rev Rheumatol*. 2020;16:413-414.
21. Haberman R, Axelrad J, Chen A, et al. Covid-19 in immune-mediated inflammatory diseases—case series from New York. *N Engl J Med*. 2020;383(1):85-88.
22. Manjili RH, Zarei M, Habibi M, Manjili MH. COVID-19 as an acute inflammatory disease. *J Immunol*. 2020;205(1):12-19.
23. Leonardi M, Horne AW, Vincent K, Sinclair J, et al. Self-management strategies to consider to combat endometriosis symptoms during the COVID-19 pandemic. *Hum Reprod Open*. 2020;2020(2):hoaa028.
24. Moazzami B, Chaichian S, Samie S, et al. Does endometriosis increase susceptibility to COVID-19 infections? A case–control study in women of reproductive age. *BMC Women's Health*. 2021;21:119.

25. American Society for Reproductive. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997;67:817-821.
26. Guerriero S, Condous G, van den Bosch T, et al. Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. *Ultrasound Obstet Gynecol*. 2016;48:318-332.
27. Guerriero S, Ajossa S, Orozco R, et al. Accuracy of transvaginal ultrasound for diagnosis of deep endometriosis in the rectosigmoid: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2016;47:281-289.
28. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. *Nat Rev Endocrinol*. 2019;15(11):666-682.
29. Goncalves MO, Siufi Neto J, Andres MP, Siufi D, de Mattos LA, Abrao MS. Systematic evaluation of endometriosis by transvaginal ultrasound can accurately replace diagnostic laparoscopy, mainly for deep and ovarian endometriosis. *Hum Reprod*. 2021;36(6):1492-1500.
30. Endometriosis: diagnosis and management. NICE guideline. September 2017.
31. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: a federated electronic medical record analysis. *PLoS Med*. 2020;17(9):e1003321.
32. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
33. Artino AR Jr, La Rochelle JS, Dezee KJ, Gehlbach H. Developing questionnaires for educational research: *AMEE guide No. Med Teach*. 2014;87(6):463-474.
34. Behzad S, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: radiologic and clinical overview. *Clin Imaging*. 2020;66:35-41.
35. Yalçın Bahat P, Kaya C, Selçuki NFT, Polat İ, Usta T, Oral E. The COVID-19 pandemic and patients with endometriosis: a survey-based study conducted in Turkey. *Int J Gynaecol Obstet*. 2020;151(2):249-252.
36. Leonardi M, Horne AW, Vincent K, et al. Self-management strategies to consider to combat endometriosis symptoms during the COVID-19 pandemic. *Hum Reprod Open*. 2020;2020(2):hoaa028.
37. Rosielle K, Bergwerff J, Schreurs AMF, et al. The impact of the COVID-19 pandemic on infertility patients and endometriosis patients in the Netherlands. *Reprod Biomed Online*. 2021. S1472-6483(21)00285-6.
38. Schwab R, Anić K, Stewen K, et al. Pain experience and social support of endometriosis patients during the COVID-19 pandemic in Germany—results of a web-based cross-sectional survey. *PLoS One*. 2021;16(8):e0256433.
39. Nezhat C, Lindheim SR, Backhus L, et al. Thoracic endometriosis syndrome: a review of diagnosis and management. *J Soc Laparoendosc Surg*. 2019;23. e2019.00029.
40. Visouli AN, Darwiche K, Mpakas A, et al. Catamenial pneumothorax: a rare entity? Report of 5 cases and review of the literature. *J Thorac Dis*. 2012;4(1):17-31.
41. Yang J, Hu J, Zhu C. Obesity aggravates COVID-19: a systematic review and meta-analysis. *J Med Virol*. 2021;93(1):257-261.
42. Patanavanich R, Glantz SA. Smoking is associated with COVID-19 progression: a meta-analysis. *Nicotine Tob Res*. 2020;22(9):1653-1656.
43. Kashyap VK, Dhasmana A, Massey A, et al. Smoking and COVID-19: adding fuel to the flame. *Int J Mol Sci*. 2020;21(18):6581.
44. Ejaz H, Alsrhani A, Zafar A, et al. COVID-19 and comorbidities: deleterious impact on infected patients. *J Infect Public Health*. 2020;13(12):1833-1839.
45. Perrotta F, Corbi G, Mazzeo G, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. *Aging Clin Exp Res*. 2020;32(8):1599-1608.
46. Popkin BM, Du S, Green WD, et al. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. *Obes Rev*. 2020;21(11):e13128.
47. Sampson JA. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol*. 1927;14:422-469.
48. Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet Gynecol*. 1984;64:151-154.
49. D'Hooghe TM, Bambra CS, Suleman MA, Dunselman GA, Evers HL, Koninckx PR. Development of a model of retrograde menstruation in baboons (Papio anubis). *Fertil Steril*. 1994;62:635-638.
50. Badawy SZ, Cuenca V, Marshall L, Munchback R, Rinas AC, Coble DA. Cellular components in peritoneal fluid in infertile patients with and without endometriosis. *Fertil Steril*. 1984;42:704-708.
51. Somigliana E, Vigano P, Gaffuri B, Guarneri D, Busacca M, Vignali M. Human endometrial stromal cells as a source of soluble intercellular adhesion molecule (ICAM)-1 molecules. *Hum Reprod*. 1996;11:1190-1194.
52. Wingfield M, Macpherson A, Healy DL, Rogers PA. Cell proliferation is increased in the endometrium of women with endometriosis. *Fertil Steril*. 1995;64:340-346.
53. Liu YG, Tekmal RR, Binkley PA, Nair HB, Schenken RS, Kirma NB. Induction of endometrial epithelial cell invasion and c-fms expression by transforming growth factor beta. *Mol Hum Reprod*. 2009;15:665-673.
54. Wu M-Y, Yang J-H, Chao K-H, Hwang J-L, Yang Y-S, Ho H-N. Increase in the expression of killer cell inhibitory receptors on peritoneal natural killer cells in women with endometriosis. *Fertil Steril*. 2000;74:1187-1191.
55. Hever A, Roth RB, Hevezi P, et al. Human endometriosis is associated with plasma cells and overexpression of B lymphocyte stimulator. *Proc Natl Acad Sci USA*. 2007;104:12451-12456.
56. Gorai I, Ishikawa M, Onose R, Hirahara F, Minaguchi H. Antiendometrial autoantibodies are generated in patients with endometriosis. *Am J Reprod Immunol*. 1993;29:116-123.
57. Porpora MG, Scaramuzzino S, Sangiuliano C, et al. High prevalence of autoimmune diseases in women with endometriosis: a case-control study. *Gynecol Endocrinol*. 2020;36(4):356-359.
58. Moghaddam MZ, Ansariniya H, Seifati SM, Zare F, Fesahat F. Immunopathogenesis of endometriosis: an overview of the role of innate and adaptive immune cells and their mediators. *Am J Reprod Immunol*. 2022;87(5):e13537.
59. Lousse J-C, Van Langendonckt A, González-Ramos R, Defrère S, Renkin E, Donnez J. Increased activation of nuclear factor-kappa B (NF-KB) in isolated peritoneal macrophages of patients with endometriosis. *Fertil Steril*. 2008;90:217-220.
60. Symons LK, Miller JE, Kay VR, et al. The immunopathophysiology of endometriosis. *Trends Mol Med*. 2018;24:748-762.
61. Singh SP, Pritam M, Pandey B, Yadav TP. Microstructure, pathophysiology, and potential therapeutics of COVID-19: a comprehensive review. *J Med Virol*. 2021;93(1):275-299.
62. Mohamadian M, Chiti H, Shoghli A, Biglari S, Parsamanesh N, Esmaeilzadeh A. COVID-19: virology, biology and novel laboratory diagnosis. *J Gene Med*. 2021;23(2):e3303.
63. Lee S, Channappanavar R, Kanneganti TD. Coronaviruses: innate immunity, inflammasome activation, inflammatory cell death, and cytokines. *Trends Immunol*. 2020;41(12):1083-1099.
64. Rydyznski Moderbacher C, Ramirez S, Dan J, et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. *Cell*. 2020;183:996-1012. e19.
65. Antsiferova YS, Sotnikova NY, Posiseeva LV, Shor AL. Changes in the T-helper cytokine profile and in lymphocyte activation at the systemic and local levels in women with endometriosis. *Fertil Steril*. 2005;84:1705-1711.

66. Gogacz M, Winkler I, Bojarska-Junak A, et al. Increased percentage of Th17 cells in peritoneal fluid is associated with severity of endometriosis. *J Reprod Immunol*. 2016;117:39-44.
67. Azar M, Shin J, Kang I, Landry M. Diagnosis of SARS-CoV-2 infection in the setting of cytokine release syndrome. *Expert Rev Mol Diagn*. 2020;20(11):1087-1097.
68. Sun Y, Dong Y, Wang L, et al. Characteristics and prognostic factors of disease severity in patients with COVID-19: the Beijing experience. *J Autoimmun*. 2020;112:102473.
69. Vassallo M, Manni S, Pini P, et al. Patients with Covid-19 exhibit different immunological profiles according to their clinical presentation. *Int J Infect Dis*. 2020;101:174-179.
70. Liu Y, Sawalh AH, Lu Q. COVID-19 and autoimmune diseases. *Curr Opin Rheumatol*. 2021;33(2):155-162.
71. Pascolini S, Vannini A, Deleonardi G, et al. COVID-19 and immunological dysregulation: can autoantibodies be useful?. *Clin Transl Sci*. 2020;14(2):502-508.
72. Keckstein J, Saridogan E, Ulrich UA, et al. The #Enzian classification: a comprehensive non-invasive and surgical description system for endometriosis. *Acta Obstet Gynecol Scand*. 2021;00:1-11.
73. Haas D, Shebl O, Shamiyeh A, Oppelt P. The rASRM score and the Enzian classification for endometriosis: their strengths and weaknesses. *Acta Obstet Gynecol Scand*. 2013;92(1):3-7.
74. Haas D, Oppelt P, Shebl O, Shamiyeh A, Schimetta W, Mayer R. Enzian classification: does it correlate with clinical symptoms and the rASRM score?. *Acta Obstet Gynecol Scand*. 2013;92(5):562-566.

How to cite this article: Barretta M, Savasta F, Pietropaolo G, Barbasetti A, Barbera V, Vignali M. COVID-19 susceptibility in endometriosis patients: A case control study. *Am J Reprod Immunol*. 2022;e13602. https://doi.org/10.1111/aji.13602