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The Impact of the COVID-19 Pandemic on Endometrial Features in Outpatient Hysteroscopy among Infertile Patients: A Retrospective Cohort Study in Southwestern Iran

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ABSTRACT

Background & Objective: Investigating the impact of COVID-19 on endometrial features in infertile patients through outpatient hysteroscopy provides a deeper understanding of the potential effects of COVID-19 on endometrial structure and function in the context of infertility. This study aimed to evaluate the impact of the COVID-19 pandemic on endometrial features in infertile women undergoing outpatient hysteroscopy in Southwestern Iran.

Materials & Methods: A retrospective cohort study was conducted in Ahvaz, Southwest Iran, comparing 250 infertile women who underwent hysteroscopy before the pandemic (February 2018–February 2020) with 250 women after the pandemic onset (March 2020–February 2022). Endometrial morphological characteristics, including vascularity, uniformity, and presence of lesions, were assessed. The two groups were compared using independent-samples t-tests and chi-square tests.

Results: The study revealed significant increases in endometrial abnormalities following the COVID-19 pandemic. Hemorrhagic lesions rose from 0.40% to 10.40% ($p < 0.001$), punctate spots increased from 0.40% to 18.00% ($p < 0.001$), and diffuse endometrial patches appeared in 19.20% of post-pandemic patients but were absent pre-pandemic ($p < 0.001$). Among post-pandemic patients, endometrial abnormalities were most prevalent in those with less than six months between COVID-19 infection and hysteroscopy, although associations were not statistically significant.

Conclusion: The findings suggest that the COVID-19 pandemic may have contributed to notable changes in endometrial morphology among infertile women, potentially due to systemic effects of SARS-CoV-2 or indirect consequences of healthcare disruptions during the pandemic. Further longitudinal and multicenter studies are needed to elucidate the underlying mechanisms and long-term reproductive health implications of these changes.

Keywords: COVID-19, Endometrium, Infertility, Hysteroscopy, Reproductive Health

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1. Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has profoundly affected various aspects of human life, including public and individual health (1, 2). While initial attention focused on acute respiratory symptoms and systemic complications of the disease, recent research has revealed that the effects of COVID-19 extend beyond the respiratory system, potentially influencing multiple organs, including the reproductive system (3, 4).

Among these effects, the impact of COVID-19 on fertility, particularly on the structure and function of the endometrium, has garnered significant attention (5). The

endometrium, the inner lining of the uterus, plays a crucial role in fertility, embryo implantation, and maintaining pregnancy (6, 7). Studies have demonstrated that ACE2 receptors, used by SARS-CoV-2 to enter cells, are also present in endometrial tissue. This finding raises the possibility of direct viral effects on the endometrium (8, 9).

Preliminary research suggests that COVID-19 infection may lead to changes in endometrial structure and function. These changes could include inflammation, alterations in endometrial thickness, menstrual cycle irregularities, and modifications in gene expression related to embryo receptivity. Importantly, these disruptions may persist even after recovery from the acute phase of illness, potentially affecting egg quality and fertility for months (10-12).

Outpatient hysteroscopy, a minimally invasive diagnostic procedure, provides a valuable tool for directly examining endometrial features. This method enables clinicians to detect subtle structural and visual changes in the endometrium that might not be apparent through conventional imaging techniques (13).

Endometrial abnormalities observed after the COVID-19 pandemic, such as increased hemorrhagic lesions, punctate spots, and diffuse patches, may negatively affect fertility by disrupting the endometrial environment and reducing embryo implantation rates. These changes could also impact the success of infertility treatments. Clinically, such abnormalities might require treatment adjustments to improve outcomes. Long-term follow-up of patients to assess treatment response and pregnancy outcomes would provide valuable insights into the effect of these changes on reproductive prognosis and help optimize therapy. Since this study lacked follow-up, future research should investigate how these endometrial alterations impact treatment success and pregnancy rates over time.

The investigation of COVID-19's impact on endometrial features in infertile patients through outpatient hysteroscopy provides a deeper understanding of the potential effects of COVID-19 on endometrial structure and function in the context of infertility. The findings from this study may contribute to improving diagnostic and therapeutic strategies for infertile patients in the post-pandemic era, addressing a critical gap in our knowledge of COVID-19's long-term reproductive health implications.

2. Materials and Methods

This study was a retrospective cohort analysis comparing endometrial morphological characteristics in infertile women before and after the COVID-19 pandemic. The study population consisted of two groups of infertile women: the first group included 250 women who visited the infertility fellowship clinic for outpatient hysteroscopy from February 2018 to February 2020 (two years before the pandemic), and the second group included 250 women who visited from March 2020 to February 2022 (two years after the start of the pandemic). These patients were women with primary and secondary infertility due to female factor infertility. The selection of patients from the pre-COVID-19 pandemic period (February 2018 to February 2020) as the non-exposed group was intended to prevent the inclusion of unidentified infection cases in the study. This approach was adopted to minimize the risk of selection bias and enhance the internal validity of the study. This method ensured that the non-exposed group was truly free of COVID-19 infection, allowing for a more accurate comparison between the two groups.

The inclusion criteria for the study were the absence of endometrial cancer, undergoing outpatient hysteroscopy at the infertility fellowship clinic, and the availability of complete patient information. Exclusion criteria included a history of abnormal endometrial lesions and acute pelvic inflammation at the time of presentation.

For data collection, the required information was gathered through a careful review of patients' medical records. For this purpose, a standardized checklist was designed that included all variables of interest in the study. The main variables examined in this study included endometrial morphological characteristics, such as vascularity, uniformity, and the presence of lesions (e.g., polyps and submucosal fibroids). In the post-pandemic group, in addition to these factors, COVID-19–related variables, including the time interval between COVID-19 infection and hysteroscopy and the time interval between COVID-19 vaccination and hysteroscopy, were also considered. It should be noted that COVID-19–positive cases only included patients who had a positive RT-PCR test result.

For hysteroscopy, a hysteroscope with a lens (UB pack) was used, having a diameter of 3.5 mm. This procedure was performed on an outpatient basis, without pain and without the need for anesthesia at the infertility fellowship clinic. All hysteroscopies were performed by an experienced specialist to ensure consistency in evaluations.

In the statistical analysis, endometrial morphological characteristics were first compared between the pre- and post-pandemic groups. Then, in the post-pandemic group, the relationship between COVID-19–related variables and endometrial characteristics was examined. For comparison of quantitative variables, the independent t-test was used. For qualitative variables, the chi-square test or Fisher's exact test was used. Data were analyzed using Stata version 17. The significance level was considered to be a p-value of less than 0.05.

3. Result

In this study, 250 patients in the pre-COVID-19 group were compared with 250 patients in the post-COVID-19 group. The results showed no significant differences between the two groups in terms of demographic and clinical characteristics. The mean age was similar in the pre-COVID-19 group (34.82 ± 5.50 years) and the post-

COVID-19 group (34.69 ± 5.18 years) (p = 0.79). BMI also showed no significant difference (26.66 ± 3.19 vs. 26.30 ± 4.21 kg/m², p = 0.27). The history of infertility medication use was slightly higher in the pre-COVID-19 group (70.0%) compared to the post-COVID-19 group (64.80%), but this difference was not significant (p = 0.22) (Table 1).

Notably, none of the patients in either group had a history of abnormal endometrial lesions. Despite this, the results revealed significant increases in several endometrial abnormalities following the COVID-19 pandemic. Hemorrhagic lesions in the endometrium rose dramatically from 0.40% to 10.40% (p < 0.001), punctate spots increased from 0.40% to 18.00% (p < 0.001), and diffuse endometrial patches appeared in 19.20% of post-COVID-19 patients, while absent in the pre-COVID-19 group (p < 0.001). Endometrial polyps showed a slight, non-significant increase from 26.40% to 29.20% (p = 0.49), while submucosal fibroids decreased non-significantly from 11.65% to 7.20% (p = 0.09) (Table 2).

Table 3 presents the distribution of endometrial morphological features in infertile women based on the time interval between hysteroscopy and COVID-19 infection. The patients were divided into three groups: 48.8% (122) were infected less than 6 months before hysteroscopy, 38.4% (96) between 6–12 months, and 12.8% (32) more than 12 months prior. The table shows the frequency of hemorrhagic lesions, punctate spots, diffuse patches, endometrial polyps, and submucosal fibroids in each group. Although no statistically significant associations were observed between the time of COVID-19 infection and endometrial characteristics (all p-values > 0.05), the majority of endometrial features were most prevalent in the group infected with COVID-19 less than 6 months before hysteroscopy. This includes hemorrhagic lesions (57.69%), punctate spots (44.44%, tied with the 6–12 months group), diffuse patches (50.0%), endometrial polyps (43.84%), and submucosal fibroids (61.11%).

Table 1. Demographic and clinical characteristics of study participants.

Variable	Pre-COVID-19	Post-COVID-19	P-Value
Age (year), mean ± SD	34.82 ± 5.50	34.69 ± 5.18	0.79
BMI (Kg/m2), mean ± SD	26.66 ± 3.19	26.30 ± 4.21	0.27
History of infertility medication use, n (%)			
Yes	175 (70.0)	162 (64.80)	0.22
No	75 (30.0)	88 (35.20)	

Table 2. Hysteroscopic findings in pre-COVID-19 and post-COVID-19 groups.

Variable	Pre-COVID-19	Post-COVID-19	P-Value
Hemorrhagic lesions in the endometrium			
Yes	1 (0.40)	26 (10.40)	0.27
No	249 (99.60)	224 (89.60)	
Punctate spots in the endometrium			
Yes	1 (0.4)	45 (18.0)	<0.001
No	249 (99.6)	205 (82.0)	
Diffuse endometrial patches			
Yes	0	48 (19.20)	<0.001
No	250 (100)	202 (80.80)	
Endometrial polyp			
Yes	66 (26.40)	73 (29.20)	0.49
No	184 (73.60)	177 (70.80)	
Submucosal fibroid			
Yes	29 (11.65)	18 (7.20)	0.09
No	220 (88.35)	232 (92.80)	

Table 3. Impact of time interval between hysteroscopy and COVID-19 infection on endometrial morphological features.

Variable	Time between hysteroscopy and contracting COVID-19			P-Value
	< 6 months	6-12 mounts	>12 months	
N (%)	122 (48.8)	96 (38.4)	32 (12.8)	
Hemorrhagic lesions in the endometrium				
Yes	15 (57.69)	5 (19.23)	6 (23.08)	0.06
No	107 (47.77)	91 (40.63)	26 (11.61)	
Punctate spots in the endometrium				
Yes	20 (44.44)	20 (44.44)	5 (11.11)	0.65
No	102 (49.76)	76 (37.07)	27 (13.17)	
Diffuse endometrial patches				
Yes	24 (50.0)	21 (43.75)	3 (6.25)	0.29
No	98 (48.51)	75 (37.13)	29 (14.36)	
Endometrial polyp				
Yes	32 (43.84)	31 (42.47)	10 (13.70)	0.6
No	90 (50.85)	65 (36.72)	22 (12.43)	
Submucosal fibroid				
Yes	11 (61.11)	5 (27.78)	2 (11.11)	0.55
No	111 (47.84)	91 (39.22)	30 (12.93)	

4. Discussion

This retrospective cohort study aimed to investigate the impact of the COVID-19 pandemic on endometrial characteristics in outpatient hysteroscopy among infertile patients. The findings of this study showed that the COVID-19 pandemic was associated with an increase in endometrial abnormalities, including hemorrhagic lesions, punctate spots, and diffuse endometrial patches. Following the COVID-19 pandemic, certain endometrial abnormalities, including hemorrhagic lesions, punctate spots, and diffuse endometrial patches, increased. Consistent with the findings of this study, the results of Bogani et al (16) also showed that the COVID-19 pandemic had a significant impact on the characteristics and care patterns of patients with endometrial cancer (16). Additionally, Karakus's study (17) found a significant decrease in proliferative endometrium and an increase in endometrial polyps among patients with menstrual irregularities after the COVID-19 pandemic (17). The excessive inflammation caused by COVID-19 may lead to changes in endometrial tissue and potentially increase the risk of endometrial polyps.

Henarejos-Castillo et al (18) also demonstrated that COVID-19 affects key fertility processes, including protection against oxidative damage, immune function, embryo implantation, and early growth. In the same context, existing evidence suggests an increase in angiotensin-converting enzyme 2 following COVID-19 infection. Molecular studies also indicate an increase in this enzyme in endometrial epithelial cells and stromal cells during the proliferative phase of the menstrual cycle, which further increases during the secretory phase and affects embryo implantation and the development of the placenta (19).

The results of a meta-analysis in 2022 showed that the COVID-19 pandemic undoubtedly led to worsening symptoms such as dysmenorrhea, pelvic pain, anxiety, depression, and fatigue in patients with endometriosis (20). While direct infection of endometrial tissue by the virus remains speculative, it raises questions about potential local inflammatory responses that contribute to changes in endometrial pathology. However, although evidence does not confirm the presence of the virus in the endometrium, this finding does not rule out tissue changes resulting from systemic effects of COVID-19 (21).

The reason for the increase in clinical symptoms such as pelvic pain, dysmenorrhea, and dyspareunia during the COVID-19 pandemic remains unclear. However, there is evidence of increased oxidative stress resulting from the renin–angiotensin–aldosterone system cascade, leading to inflammation, vasoconstriction, and endothelial dysfunction, which can cause pain (20).

Plotti et al (22), in their study comparing data before and after the pandemic, found that the COVID-19 pandemic had no direct impact on diagnostic delays, treatment types, or tumor staging. Additionally, no direct

effect was observed on endometrial cancer patterns (22). The researchers attributed the probable difference in results between this study and previous ones to the absence of diagnostic delays and the rapid treatment provided in their healthcare center. However, definitive conclusions require larger, multicenter studies.

The results of Bilgi et al (23) study in Turkey also showed a statistically significant difference in the clinical pathology of endometrial cancer before and after the COVID-19 pandemic (23). It is believed that COVID-19 affects the female reproductive system by altering endometrial tissue (24). This worsening of symptoms could be directly attributed to SARS-CoV-2 infection or indirectly due to resource and service shortages, or a combination of both (20).

One of the indirect consequences of the COVID-19 pandemic was limited access to healthcare services (25). The pandemic significantly disrupted clinical practices in women's health and routine care for endometriosis; many centers temporarily suspended outpatient services, surgeries for endometriosis, infertility treatments, and diagnostic imaging for non-acute pelvic pain (26). This could be a probable reason for the increased reporting of endometrial clinical manifestations during this period.

The findings of Barretta et al's study (27) showed that endometriosis increases susceptibility to COVID-19. However, Moazzami et al (19), in a case-control study examining the effect of endometriosis on the risk of COVID-19 infection in two groups of women with and without endometriosis, found that endometriosis does not increase the risk of COVID-19 infection, but the frequency of rare clinical manifestations such as gastrointestinal, skin, hematologic, and neurological disorders was higher in patients with endometriosis.

The difference in results among studies could stem from differences in baseline conditions of patients in the control groups across studies. Consistent with the findings of the present study, the incidence of submucosal fibroids in the case group decreased during the COVID-19 period, although this change was not statistically significant. The results of Bilgi et al's study (23) in Turkey also showed no statistical difference between the two groups of patients before and after the COVID-19 pandemic regarding age, stage, lymphovascular space invasion, muscular invasion, interstitial invasion, and tumor size, which aligns with our study (23).

However, further molecular studies are needed to elucidate the exact mechanisms underlying these findings. Patients may have paid less attention to symptoms related to changes in their reproductive system during the pandemic, and endometrial changes may have been identified at a more advanced stage. Similarly, the results of Plotti et al's study (22) attributed reduced access to regular women's check-ups to changes in endometrial pathology.

In the present study, examining the effect of the time interval between COVID-19 infection and hysteroscopy on endometrial characteristics, the most notable changes were observed in the group with less than 6 months since their COVID-19 infection, although these changes were not statistically significant. Consistent with these findings, the results of a systematic review showed that endometriosis does not exacerbate the risk of COVID-19 infection; however, the findings indicated that COVID-19 altered healthcare for endometriosis patients (28).

Additionally, Liu et al (29) findings showed that during the COVID-19 pandemic, a higher proportion of patients with endometriosis presented with chronic pelvic pain, dysmenorrhea, and more severe pain, which could be related to psychological issues following the pandemic. Xholli et al (30) findings also showed that long-term COVID-19 symptoms were more common in women with endometriosis/adenomyosis than in women without endometriosis. However, the lack of further evidence on the impact of COVID-19 infection duration on endometrial tissue changes limits further discussion.

Based on the findings of the present study, it is essential to identify how the pandemic affects different patterns of endometrial changes. However, what is clear is that early detection of factors related to endometrial changes can improve the prognosis of these changes. This study, like others, has limitations; these include the inherent bias associated with the retrospective design of the study and the selection of participants from a single healthcare center, which limits the generalizability of the results to a broader population. Additionally, the lack of long-term follow-up of study samples is another limitation. Furthermore, various confounding factors, such as stress, lifestyle changes, and other health conditions, may also play a role in endometrial changes. Distinguishing the impact of COVID-19 from these factors can be challenging. In this context, conducting longitudinal studies with larger sample sizes and in a multicenter setting is recommended.

5. Conclusion

The significant increase in endometrial abnormalities during the COVID-19 pandemic highlights the complex impact of this pandemic on women's health. Understanding these changes is crucial for developing effective clinical strategies to support women's reproductive health during and after the COVID-19 pandemic. Therefore, further research is necessary to elucidate the precise mechanisms of these pathological changes and to develop targeted interventions to reduce the impact of future pandemics on women's reproductive health.

6. Declarations

6.1 Acknowledgments

The authors would like to express our sincere gratitude to the Deputy of Research and Technology at Ahvaz Jundishapur University of Medical Sciences for providing the necessary ethical approval for this study.

6.2 Ethical Considerations

Ethical approval for this study was granted by the Ethics Committee of Jundishapur University of Medical Sciences (approval code: IR.AJUMS.REC.1403.622).

6.3 Authors' Contributions

F.M. supervised all aspects of the research, conceptualized the study design, developed the research framework, conducted data analysis and interpretation, and composed the initial manuscript. R.N. supported the study design, contributed to data acquisition, and provided critical revisions to the manuscript. Z.K. participated in data collection, performed statistical analyses, and assisted in drafting the manuscript. Z.B. coordinated data collection, prepared preliminary manuscript drafts, and handled correspondence. All authors reviewed, edited, and approved the final version of the manuscript.

6.4 Conflict of Interest

The authors declare that they have no any conflict of interest.

6.5 Fund or Financial Support

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6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

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