Cervicovaginal COVID-19 Positivity: A Pilot Study

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Research Article

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Abstract

Purpose: ACE 2 RNA expression has been detected in organs of the female reproductive tract, suggesting that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could potentially infect female reproductive organs. In this study, we investigated the presence of SARS-CoV-2 virus in the cervicovaginal fluid.

Materials and Methods: Our study included 31 female patients aged 18–65 years. The presence of SARS-COV-2 RNA was investigated by RT-PCR in two separate cervicovaginal swab samples collected from patients 14 days apart. Viral RNA was extracted using viral nucleic acid buffer (vNAT) solution, and SARS-COV-2 RNA was analyzed using Bio-speedy SARS-CoV-2 RT-qPCR kits in Bio-Rad CFX96 Touch^{TM} device.

Results: The first and second cervical swab samples were collected from 22 of 31 patients 14 days apart. The first cervical swab sample was collected from 9 patients; however, the second swab sample could not be collected after 14 days. SARS-COV-2 RNA result was negative in 100% of a total of 53 cervicovaginal swab samples collected. Moreover, the SARS-COV-2 RNA result was negative in the nasopharyngeal swab of babies after delivery in three pregnant women.

Conclusion: Negative SARS-COV-2 RNA results in cervicovaginal swab samples suggest that there is no sexual transmission of COVID-19 and no vertical transmission during pregnancy. However, the number of studies conducted on this subject and the sample size examined are still insufficient.

Introduction

COVID-19, which first emerged in December 2019, when a group of patients diagnosed with the pneumonia of unknown origin were detected in Wuhan, China [1]. The possible cause of this pneumonia was a new type of betacoronavirus. This new virus was identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the disease caused by it was named Coronavirus Disease 2019 (COVID-19) [2, 3]. On March 11, 2020, WHO declared COVID-19 a pandemic when the number of SARS-CoV-2 cases outside of China increased 13-fold with >118,000 cases and 4,000 deaths in 114 countries [4]. COVID-19 is primarily transmitted by droplets or direct contact [5, 6]. In symptomatic patients, clinical symptoms comprising fever, cough, nasal congestion, fatigue and other signs of upper respiratory tract infections usually begin in less than a week. Infection may progress to severe pneumonia with increasing shortness of breath and be fatal [7]. Although the course of COVID-19 is basically severe in the respiratory system, there are results suggesting that it affects multiple organs. In addition to lung damage, it can damage the heart, liver, kidneys and nervous system [8-12]. To date, extremely few studies have investigated the possible consequences of SARS-CoV-2 infection in male and female reproductive systems. In the literature, most studies have focused on the mechanisms leading to the development of COVID-19 disease, possible treatments and vaccine development [13]. Autopsy studies indicate that SARS-CoV-2 is transmitted to the host via direct endothelial invasion using the angiotensin converting enzyme 2 (ACE 2) receptor in various organs, including the lung, heart, kidney and intestines [14, 15]. Studies conducted before the COVID-19 pandemic have reported that ACE 2 RNA is expressed in all reproductive tissues, and the highest ACE 2

RNA levels are reported in the testicle. ACE 2 RNA expression has also detected in the prostate, vagina, fallopian tube, endometrium, and cervix. These data suggest that SARS-CoV-2 could potentially infect all male and female reproductive tissues [13]. The presence of cervical coronavirus is of great importance in terms of sexual transmission, vertical transmission in pregnant women, and reproductive medicine. The purpose of this study was to contribute to the scientific literature by investigating the presence of SARS-CoV-2 virus in the cervicovaginal fluid.

Materials And Methods

Our study included a total of 31 female patients aged 18-65 years (three of whom were pregnant) who presented to Kırşehir Education and Research Hospital between June 15 and September 1, 2020 and were RT-PCR positive for SARS-COV-2 RNA based on nasopharyngeal swab samples. The presence of SARS-COV-2 RNA was investigated by RT-PCR in two separate cervicovaginal swabs collected from the patients 14 days apart. Necessary permissions for the study were obtained from Kırşehir Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee (Decision No: 2020-08/53) and the Ministry of Health (2020-04-30T01_35_51).

Collection of Cervicovaginal Fluid Samples

Consent was obtained from the sexually active female patients whose diagnosis of COVID-19 was confirmed by nasopharyngeal SARS CoV-2 PCR test and their first degree relative. Cervicovaginal samples were collected from the patients in the presence of auxiliary health personnel while wearing appropriate personal protective equipment (N95 mask, goggles, face protection, gloves and overalls). Cervicovaginal swab samples were collected from the cervix mouth, posterior fornix and vaginal side walls by inserting a speculum while the patients were in the lithotomy position. Samples were appropriately placed in tubes containing Bio-Speedy vNAT.

SARS-COV-2 RNA Analysis

The diagnosis of patients with suspected COVID-19 presented to our hospital was confirmed by the SARS CoV-2 PCR test. Viral RNAs extracted from the nasopharyngeal swab samples using vNAT solution were analyzed by Bio-Speedy SARS-CoV-2 RT-qPCR kits (single-step reverse transcription (RT) and real-time PCR (qPCR) kit targeting ORF1ab and N gene fragments [RT-qPCR]) and Bio-Rad CFX96 Touch^{TM} device. The cervicovaginal samples collected from the patients were appropriately transferred into tubes containing Bio-Speedy viral nucleic acid buffer (vNAT) and then delivered to the microbiology laboratory as soon as possible. Viral RNAs extracted using vNAT solution were analyzed using Bio-speedy SARS-CoV-2 RT-qPCR kits and Bio-Rad CFX96 Touch^{TM} device. RT-qPCR procedure targeting the ORF1ab and N gene fragments was performed. The oligo-nucleotide set targeting the human RNase P gene (internal control) was examined for controlling sampling, nucleic acid extraction and inhibition. The internal control (IC) (RNase P) curve was marked in blue, while the SARS-CoV-2 (N) and SARS-CoV-2 (ORF1ab) curves were marked in red. When the internal control curve was a sigmoidal curve, this indicated that there was no problem regarding the sampling and isolation stages. Moreover, when the SARS-CoV-2 curve was a sigmoidal curve,

the sample was reported as POSITIVE, and when the curve was not sigmoidal, the sample was reported as NEGATIVE (**Figures 1 and 2**).

Statistical analysis

IBM SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Chi-square test was used for categorical variables, and Student's t test was used for numerical variables. The results were expressed as Mean (± SD) and N (%).

Funding

Bioeksen R&D Technologies LLC, the institution that provides SARS CoV-2 PCR tests to our hospital through the Ministry of Health, donated 100 test kits to be used in this study.

Results

A total of 31 female patients aged 20–64 years were included in the study. The mean age of the patients was 46.097 (±13.207), Gravida was 2.677 (±1,720), and parity was 2.387 (±1.801). Note that 12 (38.7%) of the patients had regular menstruation, 16 (51.7%) were in menopause, and 3 (9.6%) were pregnant. The most common accompanying chronic diseases were hypertension (n = 9, 29.0%), diabetes (n = 4, 12.9%) and chronic pulmonary disease (n = 4, 12.9%). Only 11 (35.4%) patients had COVID-19 positive spouses **(Table 1)**. Moreover, 96.7% (n, 30) of the patients had muscle and joint pain, 93.5% (n, 29) had weakness, 54.8% (n, 17) had cough, 29% (n, 9) had loss of taste, 29% (n, 9) had loss of smell, 25.8% (n, 8) had shortness of breath, and 16.1% (n, 5) had fever. Note that 27 (87.1%) patients whose overall condition was good were followed-up in the ward, and 4 (12.9%) patients whose overall condition was moderate were followed up in the intensive care unit. There were no patients with a poor overall condition to require intubation. Hydroxychloroquine + azithromycin + enoxaparin treatment was administered to 51.6% (n, 16) of patients, Hydroxychloroquine + favipiravir + enoxaparin treatment was administered to 38.7% (n, 12) of the patients, and lopinavir + ritonavir + enoxaparin treatment was administered to 9.7% (n, 3) of patients **(Table 2)**. While 77.4% (n, 24) of patients had lung involvement on CT consistent with COVID-19, 12.9% (n, 4) had no lung involvement on CT. CT was not performed for three of the patients as they were pregnant. Mean laboratory results were as follows: WBC: 5.7 (2.0-14.3), CRP: 2.2 (0.2-10.9), Ferritin: 86.7 (5.0-577.0), Troponin I: 2.3 (0.2-9.3), D-Dimer: 0.52 (0.34), and Fibrinogen: 387.3 (255.0-624.0) **(Table-3).** The patients were hospitalized for an average of 14 days for treatment and follow-up purposes. No death because of COVID-19 or any other cause was observed in the patients included in our study. Four patients in the intensive care unit were discharged with recovery after their treatment. One of the three pregnant women gave birth to a preterm baby by normal vaginal route at 34 weeks of gestation; however, the other two pregnant women gave birth to term babies by cesarean section. SARS-COV-2 RNA results was negative in nasopharyngeal swab samples of babies after birth. The preterm baby born at 34 weeks of gestation was followed up in the neonatal intensive care for ~ 1week because of prematurity. No other problem was observed afterwards. There was no evidence of COVID-19 in the one-month follow-up of babies. The first nasopharyngeal swab sample was SARS-COV-2 RNA positive in all patients (n, 31). The control

nasopharyngeal swab samples after 14 days was SARS-COV-2 RNA negative in 87.1% (n, 27) of the patients and positive in 12.9% (n, 4) of the patients. The first and second cervical swab samples were collected from 22 patients 14 days apart. The first cervical swab was collected from nine patients; however, the second swab could not be collected after 14 days. This was because they were menstruating or missed the appropriate time for sampling. SARS-COV-2 RNA result was negative in 100% of a total of 53 cervicovaginal swab samples collected **(Table 4)**.

Discussion

Coronaviruses are a single-stranded RNA virus from the Coronaviridae family of the Nidovirales virus group. The name coronavirus comes from crown-like spikes on the outer surface of virus. Coronaviruses are small 65–125-nm-sized samples. The subgroups of the coronavirus family are alpha (α), beta (β), gamma (γ) and delta (δ) coronavirus [16]. 2019-nCoV (SARS-CoV-2), a beta coronavirus, is the seventh member of the coronavirus family that infects humans after MERS-nCoV and SARS-nCoV [17]. It binds to angiotensin converting enzyme (ACE) 2 via the surface spike protein, which infects the target cell and causes severe damage similar to SARS-CoV [18, 19]. Although the lung is believed to be the target organ of 2019-nCoV, multiple non-respiratory symptoms have been reported, suggesting the involvement of other organs during the disease. ACE2 RNA expression is reported in all reproductive tissues of women (vagina, ovaries, fallopian tubes, endometrium, and cervix) and men (ductus deferens, testis, epididymis, seminal vesicle, and prostate) [13]. The study by Li et al. demonstrated that the presence of SARS-CoV-2 may be detected in semen during the active phase of the disease [20]. This suggests that SARS-CoV-2 can be sexually transmitted. Another study has reported higher ACE2 expression in male reproductive organs, particularly in the testicles; however, ACE2 expression observed in female reproductive tissues has been reported to be at lower levels. Moreover, it has the potential to infect female reproductive tissues despite low susceptibility to SARS-CoV-2 infection [13]. The first study investigating the presence of SARS-COV-2 RNA in cervicovaginal fluid was conducted by Qiu et al. This study was conducted in ten postmenopausal women aged 52–80 years hospitalized with the diagnosis of severe COVID-19. Vaginal swab samples were collected from patients 17–40 days after the onset of SARS-CoV-2 infection, and SARS-COV-2 RNA was analyzed. The presence of SARS-CoV-2 was investigated in the vaginal fluid samples of the patients. SARS-CoV-2 result was negative in all RT-PCR tests. Note that SARS-CoV-2 may have transmission mechanisms similar to SARS-CoV and that there was no report that clearly indicated that SARS-CoV invaded the female reproductive system or no reports on SARS-CoV detected in vaginal fluid. Moreover, the authors noted that the absence of SARS-CoV-2 in vaginal fluid was proof that there was no sexual transmission or no vertical transmission from mother to baby [21]. In one of the first studies on this subject, Cui et al. investigated SARS-COV-2 RNA in the cervicovaginal and anal swab samples of 35 patients diagnosed with COVID-19. Of all the samples, they detected SARS-COV-2 RNA in only one anal swab sample. All other samples were negative for SARS-COV-2 RNA. RT-PCR positivity could not be observed in the vaginal environment because of the absence of ACE2 expression, which is the SARS-CoV-2 receptor, in the tissues of the vagina and cervix. The authors noted that there was no evidence that SARS-CoV-2 was transmitted from a woman to her partner via vaginal intercourse [22]. Aslan et al. investigated the presence of SARS-COV-2 RNA in the vaginal fluid of pregnant women with COVID-19. Twelve pregnant

women with mild symptoms of confirmed COVID-19 were included in the study, and the presence of SARS-COV-2 RNA was investigated in vaginal swab samples. All samples tested negative for SARS-COV-2 RNA [23]. However, in a systematic review including 156 newborns, the vertical transmission rate was 3.91% [24]. Despite the increasing number of published studies on COVID-19 in pregnancy, there is insufficient data to draw unbiased conclusions about the complications of COVID-19, vertical transmission, and perinatal complications in pregnant women. In this study, a total of 53 cervicovaginal fluid samples were collected from 31 patients between the ages of 18-65 who were diagnosed with COVID-19 and had mild and moderate clinical symptoms. Samples were collected twice from 22 patients with an interval of 14 days, and only one time from 9 patients. SARS-COV-2 RNA was analyzed using RT-PCR method, and all samples were reported to be negative. In this study, the first samples were collected from the patients during the active disease period. The second samples were collected after 14 days. Nevertheless, all samples were negative for SARS-COV-2 RNA, which was consistent with the literature. When the perinatal results of three pregnant women in the study were evaluated, SARS-COV-2 RNA result was negative based on the nasopharyngeal swabs of the three newborns. In terms of health status, there were no results suggestive of COVID-19. The main difference of this study from other studies was that sequential samples were collected during the active disease period. Moreover, the number of patients, age range and inclusion of pregnant patients increased the observation power of the study.

Study Limitations

Although the number of patients in this study is sufficient compared to similar studies, it is still one of the primarily limitations. Another limitation is that the study was conducted in a single center. Studies on COVID-19 are rapidly continuing, and there is a requirement for comprehensive multi-center studies that include more cases.

Conclusion

Negative SARS-COV-2 RNA results in cervicovaginal swabs suggest that there is no sexual transmission of COVID-19 and no vertical transmission during pregnancy. However, the number of studies conducted on this subject and the sample size examined are still not sufficient. There is a requirement for comprehensive studies on this subject with more cases, and SARS-CoV-2 may be investigated in genital tissues using more invasive methods.

Declarations

The authors have no financial disclosures to declare.

The authors have no conflict of interest.

Ethics committee approval: Ethics committee approval was obtained from the Ahi Evran University Ethics Committee (Date: June 10, 2020 Number: 2020-08/53).

Consent to participate (Informed consent): The participants provided their signed informed consent.

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Tables

Table 1: Demographic characteristics

Age	
Mean (∓SD)	46,097(∓13,207)
Age Range	20-64
<45 (n, %)	15(48%)
≥45 (n, %)	16(52%)
Gravida	2,677(∓1,720)
Parity	2,387(∓1,801)
Menstruation	**N(%)**
Regular Menstruation	12 (%38,7)
Menopausal	16 (%51,7)
Pregnant	3 (%9,6)
Chronic Diseases	**N(%)**
None	13(%41,9)
Hypertension	9(%29,0)
Diabetes	4(%12,9)
Pulmonary Disease	4(%12,9)
Other	4(%12,9)
Employment	**N(%)**
Employed	10(%32,3)
Not Employed	21(%67,7)
COVID-19 Positivity in the Family	**N(%)**
No	9(%29,0)
Spouse	11(%35,4)
Other family members	17(%54,8)

Table 2: Clinical findings

Symptoms	**N(%)**
Muscle and Joint Pain	30(%96,7)
Weakness	29(%93,5)
Cough	17(%54,8)
Loss of Taste	9(%29)
Loss of Smell	9(%29)
Shortness of Breath	8(%25,8)
Fever	5(%16,1)
Findings	**Mean(±SD)**
Fever	36,9(±0,68)
Saturation	91,9(±5,56)
Status	**N(%)**
Good	27(%87,1)
Moderate	4(%12,9)
Poor	0
Follow-up	**N(%)**
Ward	27(%87,1)
Intensive Care	4(%12,9)
Intensive Care (Intubation)	0
Treatment	**N(%)**
Hydroxychloroquine + Azithromycin + Enoxaparin	16(%51,6)
Hydroxychloroquine + Favipiravir + Enoxaparin	12(%38,7)
Lopinavir + Ritonavir + Enoxaparin	3(%9,7)

Table 3: Imaging and laboratory results

Thoracic Tomography	N(%)	
Lung Involvement (+)	24(%77,4)	
Lung Involvement (-)	9(%12,9)	
CT not available	3(%9,7)	
Laboratory	**Mean(Min-Max)**	**Birim**
White Blood Cell	5,7(2,0-14,3)	10^3/µL
Hemoglobulin	12,7(7,8-16,8)	g/dL
Platelet	222(118-336)	10^3/µL
Glucose	105,9(61,0-292,0)	mg/dL
Urea	25,1(8,0-50,0)	mg/dL
Creatinine	0,6(0,31-1,17)	mg/dL
Aspartate Aminotransferase	26,6(13,0-42,0)	U/L
Alanine Aminotransferase	21,5(7,0-41,0)	U/L
C-Reactive Protein	2,2(0,2-10,9)	U/L
Ferritin	86,7 (5,0-577,0)	ml/ng
Troponin I	2,3(0,2-9,3)	ng/mL
D-Dimer	0,52(0,2-1,55)	ng/ml
Fibrinogen	387,3(255,0-624,0)	mg/dL

Table 4: SARS-COV-2 RNA PCR Results

Patient No	Nasopharyngeal PCR (Spouse's)	Nasopharyngeal PCR (Day 1)	Nasopharyngeal PCR (Day 14)	Cervicovaginal PCR (Day 1)	Cervicovaginal PCR (Day 14)
1*	(+)	(+)	(-)	(-)	(-)
2	(+)	(+)	(-)	(-)	(-)
3	(+)	(+)	(-)	(-)	(-)
4	(+)	(+)	(-)	(-)	0
5	(-)	(+)	(-)	(-)	0
6	(+)	(+)	(-)	(-)	(-)
7	(+)	(+)	(-)	(-)	0
8	(-)	(+)	(-)	(-)	(-)
9*	(+)	(+)	(-)	(-)	(-)
10*	(-)	(+)	(-)	(-)	(-)
11	(+)	(+)	(-)	(-)	(-)
12	(-)	(+)	(-)	(-)	(-)
13	(+)	(+)	(-)	(-)	(-)
14	(-)	(+)	(-)	(-)	0
15	(-)	(+)	(-)	(-)	0
16	(-)	(+)	(-)	(-)	0
17	(-)	(+)	(-)	(-)	(-)
18	(-)	(+)	(-)	(-)	0
19	(-)	(+)	(-)	(-)	(-)
20	(-)	(+)	(-)	(-)	(-)
21	(+)	(+)	(-)	(-)	(-)
22	(-)	(+)	(-)	(-)	(-)
23	(-)	(+)	(-)	(-)	0
24	(-)	(+)	(-)	(-)	(-)
25	(-)	(+)	(+)	(-)	(-)
26	(-)	(+)	(+)	(-)	(-)
27	(-)	(+)	(+)	(-)	(-)
28	(-)	(+)	(-)	(-)	(-)

29	(-)	**(+)**	(-)	(-)	(-)
30	(-)	**(+)**	(-)	(-)	**0**
31	**(+)**	**(+)**	**(+)**	(-)	(-)

***: Pregnant, (+): PCR Positive, (-): PCR Negative, 0: PCR analysis not available**

Figures

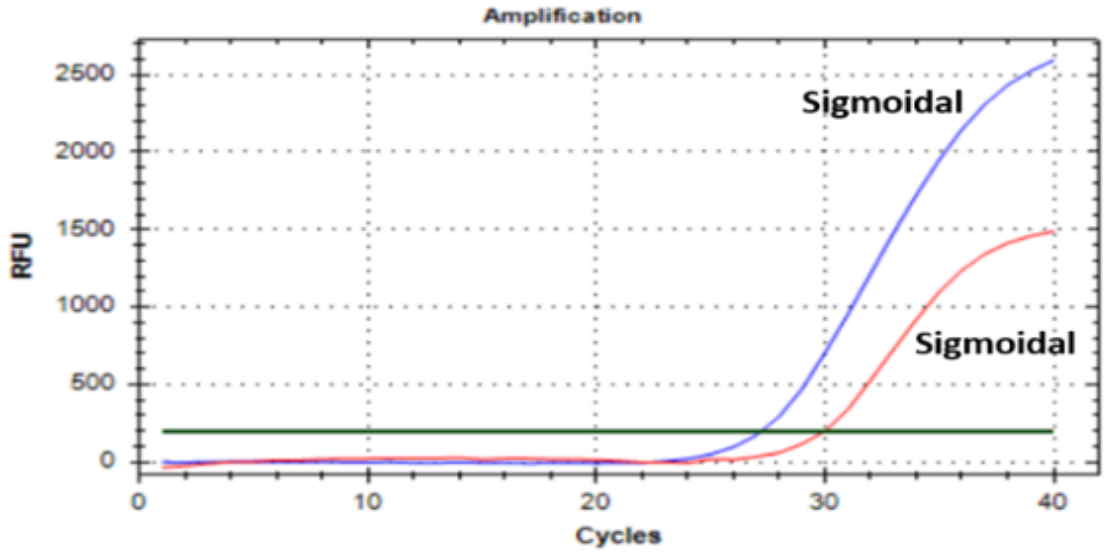

Figure 1

SARS-CoV-2 Positive Results

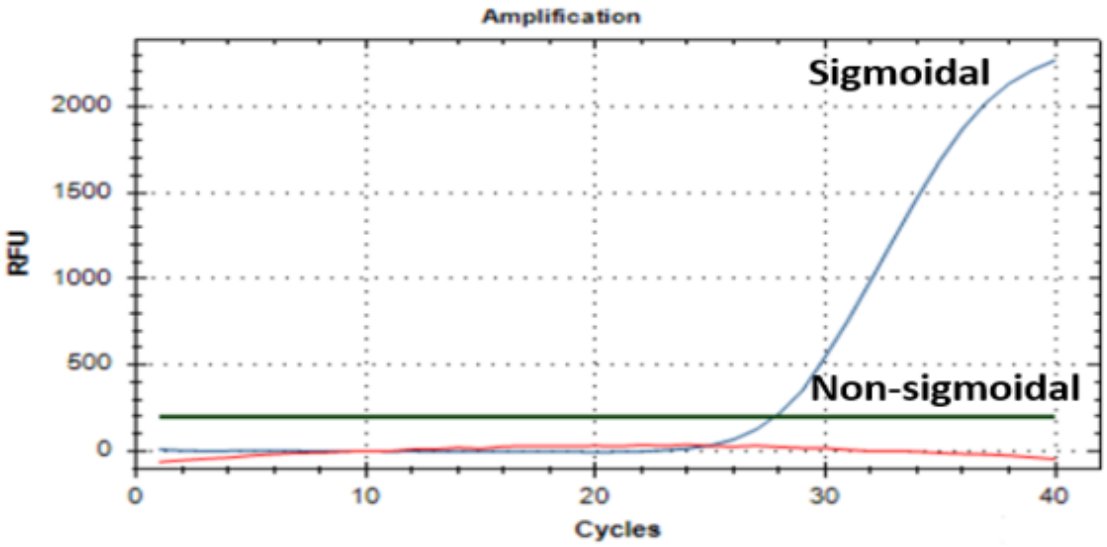

Figure 2

SARS-CoV-2 Negative Results