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# COVID-19 may affect male fertility but is not sexually transmitted: a systematic review

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**Objective:** To determine if SARS-CoV-2, which has led to the rapidly spreading COVID-19 global pandemic, is sexually transmitted. Since the putative receptor for the virus is identified in reproductive organs, it is also important to examine if COVID-19 may affect human fertility.

**Evidence Review:** A systematic review of English publications was conducted up to December 11, 2020 in PubMed, NIH iCite COVID-19 portfolio, Cochrane Library, and Google Scholar databases, searching for SARS-CoV-2 in the testes; seminal, prostatic, and vaginal fluids; and cervical smears. A total of 1,997 records were identified, duplicates were removed, and 1,490 records were reviewed for eligibility by examining titles and abstracts. Subsequently, 202 full-text relevant articles were reviewed by 2 independent reviewers. Forty-seven studies (literature reviews, editorials, and guidelines) were assessed qualitatively, and 23 studies that tested the male and female reproductive tracts of patients with COVID-19 for SARS-CoV-2 were quantitatively analyzed.

**Results:** No epidemiological investigations to date have described evidence suggesting that COVID-19 is an STD. While angiotensin-converting enzyme 2 receptor is found in the reproductive organs, the lack of co-expression of the TMPRSS2 modulatory protein, required for SARS-CoV-2 cell entry, in testicular cells, sperm, or oocytes, argues against the hypothesis that gametes transmit SARS-CoV-2. Molecular detection studies of SARS-CoV-2 RNA in the male and female reproductive tracts were summarized: 98.0% (293/299) of the seminal fluids, 16/17 testicular biopsies, all 89 prostatic fluids, 98.3% (57/58) of the vaginal fluids, all 35 cervical smears, and all 16 oocyte samples tested negative for SARS-CoV-2. None of the studies confirmed sexual transmission of SARS-CoV-2. Nonetheless, COVID-19 may have detrimental effects on male reproduction by inducing orchitis and/or decreasing testosterone levels, sperm counts, and motility.

**Conclusion:** On the basis of the current worldwide published information, COVID-19 is not an STD. This information is important for clinicians, proposed guidelines for public health, U.S. Food and Drug Administration guidelines for gamete and tissue donor eligibility, and fertility treatments. Universal precautions, currently practiced worldwide, are adequate and sufficient at this time to prevent the transmission of known or unknown viral infections. We suggest that recovered patients of COVID-19, especially those with infertility, should be evaluated for their ovarian and testicular function. (Fertil Steril Rev® 2021;2:140-9. ©2021 by American Society for Reproductive Medicine.)

**Key Words:** COVID-19, infertility, IVF, SARS-CoV-2, sexual transmission

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## ESSENTIAL POINTS

- SARS-CoV-2 has led to a fast-spreading global pandemic of COVID-19. By December 11, 2020, it has infected more than 71 million people worldwide and caused over 1.5 million deaths globally, with over 15 million infected and almost 300,000 deaths in the United States alone.
- From a public health perspective, it is important to determine if SARS-CoV-2 is sexually transmitted. To cause a sexually transmitted disease (STD), a virus has to be detected in seminal or vaginal fluids from asymptomatic or symptomatic people and transmitted through intercourse or insemination.

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- No epidemiological investigations to date have suggested that COVID-19 is an STD. The lack of co-expression of viral angiotensin-converting enzyme 2 receptors and the TMPRSS2 modulatory protein in testicular cells, sperm, and oocytes further rejects the hypothesis that gametes transmit SARS-CoV-2.
- This systematic review of available global clinical data up to December 11, 2020 regarding SARS-CoV-2 in the testes; seminal, prostatic, and vaginal fluids; cervical smears; and oocytes concludes that the virus is not sexually transmitted. This information is important for public health guidelines, U.S. Food and Drug Administration guidelines on gamete donor eligibility, and fertility treatments.
- COVID-19 may affect male fertility. Further prospective and longitudinal controlled studies are needed to investigate the potential effects of COVID-19 on human fertility.

**S**ARS-CoV-2 has led to a large-scale global pandemic of COVID-19. As of December 11, 2020, it has infected more than 71 million people worldwide and caused over 1.5 million deaths globally, with over 15 million infected and almost 300,000 deaths in the United States alone.

Coronaviruses are endemic in humans and responsible for 15%–30% of respiratory tract infections yearly. The SARS outbreak in 2002–2003 infected approximately 8,000 people worldwide, with a 9% mortality rate (1). The 2012 Middle East respiratory syndrome coronavirus outbreak infected only approximately 2,500 people but had a 35% mortality rate (2). COVID-19 clinical manifestations have been summarized by others (3–6).

While no previous coronavirus infection was reported to be a sexually transmitted disease (STD) (1, 2, 7, 8), a May 2020 scientific publication (9) reported the finding of SARS-CoV-2 RNA in the semen of 6 out of 38 patients with COVID-19, heightening concern for its potential sexual transmission (9). Furthermore, since the putative angiotensin-converting enzyme 2 (ACE2) receptor for SARS-CoV-2 was found in reproductive organs (7, 10–14), it was important to examine if the virus targets and infects the human reproductive tract and affects fertility and to resolve if it is sexually transmitted or not. It is clear that COVID-19 can be transmitted with intimate sexual contact through droplets and fomites, but from a clinical and public health perspective, it is imperative to determine if sexual transmission occurs as well.

To determine if COVID-19 is an STD or not and clarify its possible effect on fertility, we conducted a systematic review of global epidemiological investigations, molecular receptor identification, and detection studies of SARS-CoV-2 in the male and female reproductive tracts.

## MATERIALS AND METHODS

A systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15) on English literature available through PubMed, NIH iCite COVID-19 portfolio, Cochrane Library, and Google Scholar databases. Briefly, the search terms included the following: SARS-CoV-2 and/or COVID-19 with STD, STD, sperm, seminal fluid, semen fluid, semen, prostatic fluid, orchitis, testes, oocyte, ovary, vaginal fluid, cervical smear, follicular fluid, embryo, and implantation. The exact search terms are listed in the online supplement (Supplemental Table 1, available online). While the initial literature search ended on July 15, 2020, following the special pandemic circumstances and the

Editorial request, the search was extended to December 11, 2020. This updated comprehensive search found no data that changed any of the conclusions.

Sexual transmission of SARS-CoV-2 was considered if it occurred through vaginal intercourse, vaginal penetration, or insemination. Other forms of possible viral transmission or shedding, such as by blood, oral-fecal, and urine, have been discussed by others (16–23). No study documenting the transmission of SARS-CoV-2 through homosexual sexual relationships was found in our search. Articles were included if original data on SARS-CoV-2 RNA in the male or female reproductive tracts were presented, if there was a discussion of such possible sexual transmission, or if commentary regarding any COVID-19 effect on human reproduction was included.

The quality of the included studies was rated according to the Oxford Centre for Evidence-Based Medicine levels of evidence by 2 investigators independently, with discrepancies resolved after joint article review and discussion (24).

## RESULTS

The search produced a total of 1,997 records. After duplicates were removed, 1,490 records were screened and assessed for eligibility by examining titles and abstracts (by investigators T.T. and G.H.). Next, 202 full-text relevant articles were reviewed and evaluated by 2 independent reviewers (I.T. and D.C.) for inclusion in the study. After applying inclusion and exclusion criteria, 47 qualitative studies (literature reviews, editorials, and guidelines) remained, and 23 quantitative studies that tested the male and female reproductive tracts of 404 adult patients with COVID-19 for SARS-CoV-2 RNA were selected for inclusion.

The results of the literature search are detailed in the online supplement with a PRISMA-style flow diagram (Supplemental Fig. 1, available online). In total, 70 reports formed the basis of this review.

### Evidence from epidemiological investigations

For a viral infection to be labeled as an STD, virus infectivity via sexual intercourse or insemination and not just the presence of its viral particles is required (25). Classifying a viral infection as an STD requires observational epidemiological studies. The transmission of SARS-CoV-2 through respiratory droplets and aerosol has been documented, but no epidemiological investigation to date has implicated, or even suspected, sexual transmission (16, 26–31).

## Evidence for SARS-CoV-2 targeting the human reproductive tract

**Evidence for ACE2/TMPRSS2-mediated mechanism for SARS-CoV-2 cell entry.** SARS-CoV-2 uses the ACE2 receptor and cellular protease TMPRSS2 to enter the target cells. Both are essential for viral spread and disease in the infected host (32). Expression of the ACE2 receptor is identified in the ovary, vagina, uterus, and placenta of women (10, 14) and testis of men (7, 11–13). ACE2 receptor identification in the reproductive tracts led to speculation that SARS-CoV-2 might infect the gonads, be found in seminal and/or vaginal fluid, or attach to sperm and/or oocytes. Furthermore, the evidence of SARS-CoV-2-induced orchitis suggested that testicular infection might damage the testis-blood barrier and permit viral shedding into semen.

It is important to distinguish, however, between the localization of receptors, localized inflammation (orchitis), and virus infectivity. Although SARS-CoV also uses ACE2 receptors, no SARS virus was detected in the testes or vaginal fluids in pathologic specimens during the SARS epidemic in 2002–2003, even in men with pathologically documented inflammatory orchitis (8).

Because TMPRSS2 is highly expressed in the prostate, Song et al. (33) investigated TMPRSS2 and ACE2 co-expression in human prostate epithelial cells. They analyzed 24,519 epithelial cells from a normal human prostate data set using publicly available single-cell RNA sequencing data. While 18.65% of these cells expressed TMPRSS2, only 0.32% of all epithelial cells (78 of 24,519) expressed ACE2. Overall, the co-expression of ACE2 and TMPRSS2 in the prostatic cell types investigated was approximately 0.4%–0.6% (33). No SARS-CoV-2 was found in the prostatic fluid of 98 men with COVID-19 in 3 different studies, supporting the aforementioned finding of a very low co-expression of ACE2 and TMPRSS2 in the prostate (34–36).

Recently, it was reported that while the ACE2 receptor is found in reproductive organs, TMPRSS2 is not co-expressed in testicular cells, sperm, or cumulus-enclosed oocytes (may be expressed at <0.01% of the cells) (13, 32, 37). Since TMPRSS2 is required for SARS-CoV-2 cell entry, this finding suggests that SARS-CoV-2 is unlikely to enter testicular cells through an ACE2/TMPRSS2-mediated mechanism (13, 32, 37).

Furthermore, 16 oocytes from 2 asymptomatic SARS-CoV-2-positive egg donors were all negative for the viral RNA (38), and while in 5 of 16 oocytes ACE2 was detectable, TMPRSS2 was undetectable in all oocytes. Since both ACE2 and TMPRSS2 are essential for viral spread (32), these data oppose the proposition that sperm and oocytes might be infected by SARS-CoV-2 and argue that the virus is not sexually transmitted (13, 37, 39).

**Evidence for SARS-CoV-2 in the male reproductive tract.** Tables 1 and 2 depict published global studies investigating the presence of SARS-CoV-2 RNA in the male reproductive tract. Table 1 summarizes findings in the seminal fluid (9, 36, 37, 40–50), and Table 2 summarizes findings in the testes and prostatic fluid (34–36, 40, 51, 52).

Of all seminal fluids tested, 98.0% (293/299) were negative for the virus (Table 1) (9, 36, 37, 40–50). Most of these

men demonstrated mild COVID-19 symptoms (163/299), and negative results of nucleic acid testing were documented as early as 4 days after confirmed COVID-19 diagnosis. Not surprisingly, the majority of viral testing was performed in patients during disease recovery. One study, of the 14 reviewed, identified 6 men with positive seminal fluid viral RNA tests (2.0% of all the men from all 14 studies) (9). Of these 6 men, 4 were in the acute stage of infection and 2 were in recovery, between 6 and 16 days after COVID-19 diagnosis. The investigators of this outlier study (9) provided limited information on the reverse transcription polymerase chain reaction test kit they used, the test kit's limits of detection, gene targets, and cycle threshold and did not describe the semen collection protocol (9, 53). Since this positive report (9) demonstrated only molecular detection and not viral shedding, we and others (37, 40–44) agree with the investigator's (9) own assessment that their results should be confirmed by others before it influences groups formulating guidelines or clinical practice. Furthermore, in 2 other studies where testing was also obtained within the acute stage of infection, the seminal fluids of all 14 men tested negative for SARS-CoV-2 (43, 44). Interestingly, 7 men who demonstrated orchitis-like symptoms, identified in 2 of the studies, also all tested negative for SARS-CoV-2 in their seminal fluid (37, 43).

Finally, all 89 prostatic fluids tested were negative for the virus (Table 2) (34–36). One of the 17 testicular biopsies (40, 51) tested positive for SARS-CoV-2 RNA, but the investigators (51) of that study questioned their own finding, commenting that “the reverse transcription polymerase chain reaction likely detected the virus present in the blood rather than in testicular tissue” (51).

Taken together, these data suggest that SARS-CoV-2 is not sexually transmitted through sperm or semen (34–37, 40–50, 54).

## Evidence for SARS-CoV-2 in the female reproductive tract.

Table 3 presents the currently published investigations of SARS-CoV-2 RNA in the vaginal fluid, cervical smears, and human oocytes. Specifically, 98.3% (57/58) of the vaginal fluids tested negative (14, 55–57), and all 35 cervical smears tested negative for SARS-CoV-2 as well (56). Vaginal fluid testing was performed as early as 8 days after diagnosis, and most of the women (44/58) demonstrated severe COVID-19 symptoms (14, 55–57). In one study (56), while all 35 vaginal fluids tested negative, the infection rate of the patients' sexual partner was 42.9%. Interestingly, 2 women with negative vaginal fluid tests engaged in sexual activity with their partners 14 days before the onset of symptoms and continued until the day samples were collected. One of the partners tested positive for COVID-19, and the other did not (56). Only 1 woman (14) tested positive for SARS-CoV-2 RNA in the vaginal fluid out of 58 women tested in 4 studies (1.7%) (14, 55–57). This woman was 67-years-old and initially had 2 negative vaginal samples after COVID-19 diagnosis (14). After these initial negative tests, she tested positive on 2 occasions and subsequently tested negative again. There was no information about the test kit used in this case report (14).

TABLE 1

## Severe acute respiratory syndrome coronavirus 2 in the seminal fluid of men with coronavirus disease 2019.

Studies	City, country	Study type (quality rating)	Date of publication	No. of men	Mean age (range)	Mean days from diagnosis (range)	Severity of COVID-19	Seminal fluid result	Control	Reverse transcription polymerase chain reaction manufacturer
Song et al. (40)	Nanjing, China	Cohort (4)	4/16/2020	12	30 (22–38)	29 (14–42)	Asymptomatic (1/12), mild (11/12)	All negative	No	Huirui Biotechnology
Ning et al. (41)	Wuhan, China	Cohort (4)	4/16/2020 (Preprint)	17	35 (23–46)	27 (12–64)	Asymptomatic (8/17), mild (9/17)	All negative	No	Sansure Biotech
Pan et al. (37)	Wuhan, China	Cross-sectional (4)	4/17/2020	34	39 (18–55)	31 (8–75)	Mild (34/34)	All negative <sup>a</sup>	No	Anda Gene Ltd
Paoli et al. (42)	Rome, Italy	Case report (5)	4/23/2020	1	31	8	Mild (1/1)	Negative <sup>b</sup>	No	altona Diagnostics
Li et al. (9)	Shangqiu, China	Cohort (4)	5/7/2020	38	≥ 15 (NA)	11 (6–16) for the 6 men who tested positive	NA	84.2% negative (32/38) <sup>c</sup>	No	NA
Holtmann et al. (43)	Düsseldorf, Germany	Cohort control (3b)	5/29/2020	18	42 (32–52)	NA (8–54)	Mild (14/18), moderate (4/18) <sup>d</sup>	All negative	N = 14 All negative	PE Applied Biosystems
Guo et al. (44)	Shandong, China	Case Series (4)	6/29/2020	23	41 (20–62)	31 (26–34)	Mild (18/23), moderate (5/23)	All negative <sup>e</sup>	No	Huirui Biotechnology
Ma et al. (45)	Wuhan, China	Cross-sectional (4)	7/4/2020	12	31.5 (25–46)	78.5 (56–109)	Mild (1/12), moderate (11/12)	All negative	No	NA
Rawlings et al. (46)	San Diego, USA	Cross-sectional (4)	8/7/2020	6	38 (28–45)	12 (6–17)	Mild (6/6)	All negative	No	ddPCR
Pavone et al. (47)	Palermo, Italy	Cross-sectional (4)	8/14/2020	9	41 (28–52)	42 (7–88)	Asymptomatic (1/9), mild (8/9)	All negative	No	NA
Kayaaslan et al. (48)	Ankara, Turkey	Cross-sectional (4)	9/1/2020	16	33.5 (18–54)	1 (0–7)	Mild (16/16)	All negative	No	Bio-Speedy
Li et al. (49)	Wuhan, China	Cross-sectional cohort study (4)	10/23/2020	23	41 (27–55)	26 (4–42)	Mild (14/23), moderate (9/23)	All negative	N = 22 All negative	NA
Ruan et al. (36)	Wuhan, China	Cross-sectional (4)	11/4/2020	70	31 (27–36)	80 (64–93)	Mild (15%), moderate (42%), severe (43%)	All negative	No	DAAN Gene
Temiz et al. (50)	Istanbul, Turkey	Cross-sectional (4)	11/26/2020	20	37.5 (18–60)	(1–5)	Mild (20/20)	All negative	N = 10 All negative	Coyote Bioscience Co.
Total	10 cities, 5 countries	—	April to November 2020	299	36 (15–62)	31 (0–109)	Asymptomatic (10/299), mild (163/299), moderate (58/299), severe (30/299), NA (38/299)	98.0% negative (293/299), 2.0% positive (6/299)	Controls: Negative (46/46)	—

Note: NA = not available or not reported.

<sup>a</sup> Six men had orchitis during the time of infection and all tested negative (37).

<sup>b</sup> Urine was collected and tested on the same day as the seminal fluid and also tested negative (42).

<sup>c</sup> Of the 6 positive patients, 4 were at the acute stage of infection, and 2 were in recovery (9).

<sup>d</sup> Subjects with a moderate infection demonstrated impaired sperm quality (43).

<sup>e</sup> The sperm counts, motility, and morphology of the patients were within the normal range (44).

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TABLE 2

## Severe acute respiratory syndrome coronavirus 2 in the testes or prostatic fluid of men with coronavirus disease 2019.

Sample tested	Studies	City, country	Study type (quality rating)	Date of publication	No. of men	Mean age (range)	Mean days from diagnosis (range)	Severity of COVID-19	Results	Control	Reverse transcription polymerase chain reaction manufacturer
Testes	Song et al. (40)	Nanjing, China	Cohort (4)	4/16/2020	1	67	42	Deceased (1/1)	Testicular biopsy: negative	No	Huirui Biotechnology
	Yang et al. (51)	Wuhan, China	Case series (4)	5/26/2020	10	65 (42–87)	42 (23–75)	Deceased (10/10)	Testicular biopsy: 90.0% negative (9/10) <sup>a,b</sup>	No	Liferiver Biotechnology
	Achua et al. (52)	New York City, USA	Case series (4)	11/30/2020	6	49.5 (22–83)	15 (7–27)	Deceased (6/6)	Testicular biopsy: all negative	No	NA
	<b>Total</b>	3 cities, 2 countries	—	April to November 2020	17	60.5 (22–87)	33 (7–75)	Deceased (17/17)	Testicular biopsy: 94.1% negative (16/17), 5.9% positive (1/17)	No	—
Prostatic fluid	Quan et al. (34)	Shenzhen, China	Cohort (4)	3/30/2020 (preprint)	18	60 (20–60+)	NA (3–14+)	Mild (18/18)	Prostatic fluid: all negative	N = 5 all negative	BGI
	Zhang et al. (35)	Wuhan, China	Case series (4)	6/10/2020	10	57 (29–76)	11 (8–17)	Mild (10/10)	Prostatic fluid: all negative	No	NA
	Ruan et al. (36)	Wuhan, China	Cross-sectional (4)	11/4/2020	61	31 (27–36)	80	Mild (15%), moderate (42%), severe (43%)	Prostatic fluid: all negative	No	DAAN Gene
	<b>Total</b>	2 cities, 1 country	—	March to November 2020	89	49 (20–76)	45.5 (3–17)	Mild (37/89), moderate (26/89), severe (26/89)	Prostatic fluid: 100% negative (89/89)	Negative (5/5)	—

Note: NA = not available or not reported.

<sup>a</sup> For the one positive testicular biopsy for SARS-CoV-2, the investigators concluded “it is likely that reverse transcription polymerase chain reaction detected the virus present in blood rather than in testicular tissue” (51).

<sup>b</sup> Electron microscopy of testicular tissue for 3 of the reverse transcription polymerase chain reaction-negative patients failed to identify viral particles (51).

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TABLE 3

Severe acute respiratory syndrome coronavirus 2 in the reproductive tract of women with coronavirus disease 2019: in vaginal fluid, cervical smear, and oocytes.

Studies	City, country	Study type (quality rating)	Date of publication	No. of women	Mean age (range)	Mean days from diagnosis (range)	Severity of COVID-19	Vaginal fluid result	Cervical smear result	Oocyte result	Control	Reverse transcription polymerase chain reaction manufacturer
Qiu et al. (55)	Wuhan, China	Cohort (4)	4/2/2020	10	66 (52–80)	28 (17–40)	Severe (10/10)	All negative	NA	NA	No	NA
Scorzolini et al. (14)	Rome, Italy	Case report (5)	4/16/2020	1	65	NA	NA	Initially negative/then positive/then negative	NA	NA	No	NA
Cui et al. (56)	Wuhan, China	Cohort (4)	5/3/2020	35	62 (37–88)	23 (8–41) <sup>a</sup>	Severe (34/35)	All negative	All negative	NA	No	DAAN Gene and BioPerfectus Technologies
Aslan et al. (57)	Sakarya, Turkey	Cross-sectional (4)	7/5/2020	12 <sup>b</sup>	32 (24–40)	NA	Mild (12/12)	All negative	NA	NA	No	NA
Total	3 cities, 3 countries	—	April to July 2020	58	56 (24–88)	26 (8–41)	Mild (12/12), severe (44/58), NA (1/58)	98.3% negative (57/58), 1.7% positive (1/58)	100% negative (35/35)	100% negative (2/2)	No	—
Barragan et al. (38)	Barcelona, Spain	Case report (5)	9/30/2020	2	(20–30)	NA	Asymptomatic (2/2)	NA	NA	N = 16 All negative	No	QIAGEN

Note: NA = not available or not reported.

<sup>a</sup> Twenty-seven patients were diagnosed with COVID-19 on the basis of a positive SARS-CoV-2 throat swab. The other 8 patients were diagnosed on the basis of clinical symptoms (56).<sup>b</sup> All 12 women were pregnant with an average pregnancy of 26.0 ± 10.3 weeks' gestation (57).Tur-Kaspa. COVID-19 affects fertility, not an STD. *Fertil Steril Rev* 2021.

Sixteen oocytes from 2 asymptomatic SARS-CoV-2-positive egg donors tested negative for the viral RNA (38). This report of testing human oocytes obtained during routine egg donor in vitro fertilization cycle supports the conclusion that oocytes obtained from asymptomatic women by in vitro fertilization do not transmit SARS-CoV-2.

COVID-19 during pregnancy and in neonates has been reviewed elsewhere (7, 58). To date, there is no evidence of vertical transmission of COVID-19 during vaginal birth (57–59), supporting the notion that the virus is not transmitted to newborns during vaginal delivery.

### Evidence for the impact of COVID-19 on fertility

COVID-19 might affect male fertility by damaging the endocrine function and/or by temporary or permanent changes caused by elevated body temperature and/or orchitis. The evidence of damaged endocrine function is demonstrated by significantly lower serum testosterone to luteinizing hormone ratios, a measure used as a predictor of compromised testicular function, in patients with COVID-19 compared with those in controls (17). The possible role of testosterone and estrogen affecting the prevalence of COVID-19 in men compared with that in women and their role in the disease's severity have been discussed by others (3, 4, 60).

Viral-induced testicular damage may cause hypogonadism and infertility in some men. Local inflammatory damage of the testis-blood barrier might potentially lead to indirect semen infection. A survey of 91 hospitalized patients with COVID-19 revealed 11% patients with related testicular pain, but a clinical presentation of epididymo-orchitis was diagnosed in only 1 patient (61).

Using bedside ultrasound examination of the scrotum in 142 men with a confirmed diagnosis of COVID-19, 22.5% patients were diagnosed with acute orchitis, epididymitis, or epididymo-orchitis (62). The investigators used imaging criteria for acute inflammation, including tunica albuginea thickening; enlargement and heterogeneous echogenicity of the testis, epididymis, or both; an abscess; scrotal wall edema; and hydrocele. The observed risk of acute scrotal inflammation or infection increased with the severity of COVID-19 infection and age. Interestingly, in patients <40 years old, the age of the majority of men seen for infertility, the risk of acute scrotal inflammation or infection during COVID-19 was only 6.3% compared with 25% in patients >80 years old ( $P=.003$ ) (62).

Testicular biopsies from deceased men after SARS and COVID-19 infections (40, 51) revealed only testicular inflammation and reduced spermatogenesis. Biopsies demonstrated lymphocytic inflammation, reduced spermatogenesis, and increased testicular fibrosis, but the seminiferous tubules were intact. The findings are presumed to result from the inflammatory response and not the virus directly. Furthermore, electron microscopy failed to demonstrate SARS-CoV-2 viral particles in the testis (51).

Two studies investigated semen analyses in patients recovering from COVID-19, 8–54 days after diagnosis. One study demonstrated a decreased sperm count and motility compared with controls (43), and the other study found the sperm count,

motility, and morphology to be within normal ranges (44). Since elevated body temperature has a known deleterious effect on sperm count and motility, the fever, and not the SARS-CoV-2 infection per se, might have caused the reduction in total motile sperm counts observed in some patients (39).

Thus, unless the patient has active COVID-19 and contamination from blood, urine, or feces should be avoided, in vitro fertilization treatment and embryo and gamete cryopreservation seem to pose no significant risk to the embryos produced.

In summary, COVID-19 may cause inflammation in approximately 5%–10% of men of reproductive age and, rarely, even infection of the testes. Such orchitis is highly correlated with the severity of the disease and age. Sperm and oocytes are unlikely to be susceptible to infection by SARS-CoV-2, and there is no evidence to support that COVID-19 is an STD (63).

To date, the possible effects of COVID-19 on the ovary or residual ovarian reserve have not been investigated (64). We suggest that the survivors of COVID-19, especially those suffering from infertility, should be evaluated for their short- and long-term ovarian and testicular function (54, 60, 63, 65).

## DISCUSSION

The number of infected patients and information about the clinical course of COVID-19 is increasing rapidly (3, 4). Clinicians worldwide should continue to follow national and professional guidelines and the Centers for Disease Control and Prevention, U.S. Food and Drug Administration (FDA), and World Health Organization websites to stay updated.

To determine if SARS-CoV-2 is sexually transmitted and if guidelines should be specifically updated to address this concern, this systematic review summarizes recent global data of epidemiological investigations, molecular receptor identification, and detection studies of SARS-CoV-2 RNA in the male (in testicular biopsies, seminal, and prostatic fluids) and female (in vaginal fluids, cervical smears, and oocytes) reproductive tracts. The available evidence provides no suggestion that sperm, semen, or the female genital tract transmits SARS-CoV-2 (34–37, 40–50, 55–57). A recent review of the 21st century viral pandemics (66) concurs that current evidence (9, 37, 40–42) does not support that SARS-CoV-2 is present in the semen and is therefore unlikely to be sexually transmitted. Any form of sexual intimacy worsens the risks of COVID-19 transmission (67–69), and while SARS-CoV-2 can be transmitted during sexual contact by aerosols and fomites, on the basis of currently available information, it is concluded that the virus is not sexually transmitted. There is the potential for transmission of SARS-CoV-2 via blood (16), urine (17–19), and feces or oral-fecal (20–23), and these forms of transmission have been discussed by others (16–23). Homosexual sexual practices have not been reported to transmit the virus.

The identification of viral receptors in human reproductive organs raised concerns about the vulnerability of infected gametes transmitting the virus sexually by artificial insemination or during vaginal births from mothers to newborns. While the ACE2 receptor has been identified in reproductive

organs, its co-expression with TMPRSS2, required for SARS-CoV-2 cell entry, is lacking in testicular and prostatic cells, sperm, or oocytes. This suggests that the hypothesis that sperm and oocytes may become infected by SARS-CoV-2 should be rejected; these cell types are also unlikely vectors to sexually transmit or infect an embryo (13, 37, 39). Lastly, to date, there is no evidence of vertical transmission of COVID-19 during labor (acquisition during passage through the vaginal canal) (58, 59, 66). Therefore, proposing that SARS-CoV-2 infection of reproductive tract tissues via ACE2 receptors leads to sexual or vertical transmission (10, 14) is a premature theory and is not supported by current scientific evidence.

Nonetheless, COVID-19 may have temporary or permanent detrimental effects on male reproduction. It may involve endocrine alterations in luteinizing hormone and testosterone (17) and decreased sperm parameters (43) or may induce an inflammatory orchitis resulting in fibrosis and further loss of testicular function (37, 43, 51). It is not known if, or how, it might also affect female fertility, ovarian endocrine function, or ovarian reserve. Prospective and longitudinal control studies are warranted to elucidate any possible long-term consequences of SARS-CoV-2 on human fertility.

There are several limitations for the studies reviewed. Because of the exponential rate of viral infections and the variations in international and local characteristics and responses, there remain multiple areas of testing data acquisition and interpretation uncertainty. This has led to difficulties in creating best practice protocols to prevent further spread of SARS-CoV-2. The urgency to develop testing quickly resulted in less rigorous approval processes of SARS-CoV-2 reverse transcription polymerase chain reaction test kits, varying test kit sensitivities and specificities, and diminished methodological standards for conducting studies. With a rush to publish data and supply frontline providers with data, studies are performed in locations with differing prevalence of patient infectivity using different sampling methods and a lack of controls (65). These problems synergize and make data interpretation and, more importantly, data comparisons difficult.

A major limitation of the studies that specifically tested the male and female reproductive tracts of patients with COVID-19 for SARS-CoV-2 is that, overall, the published evidence is generally considered low quality, with ratings ranging from 3b to 5 (Tables 1–3). In addition, the consequences of some study design irregularities are evident in investigations demonstrating the presence of viral RNA particles but not a contiguous virus in tissues and bodily fluids. Nonetheless, the studies included in this review consist of all of the currently published international data through December 11, 2020 and include preprints as well to maximize the inclusion of available data.

There is only 1 publication (out of 14) that describes SARS-CoV-2 RNA in the semen of 6 men (9), and in only 1 case report was SARS-CoV-2 RNA found in vaginal fluid (14). Both studies with positive results failed to provide information on the specifics of the test kits employed and neither had a control group for comparison. Moreover, the infectivity of the viral particles detected is unknown. Although all



investigations consisted of a small number of patients, they represent different populations with variable disease severity and, taken together, suggest that SARS-CoV-2 is not found in the male and female reproductive tracts.

While guidelines for the prevention of SARS-CoV-2 transmission have been published by the Centers for Disease Control and Prevention and World Health Organization (67, 68), to establish best practice guidelines, more comprehensive published evidence and systematic reviews are needed. Professional societies for infertility and reproductive medicine, including the American Society for Reproductive Medicine, European Society of Human Reproduction and Embryology, and International Federation of Fertility Societies, published a joint statement significantly revising initial recommendations regarding fertility treatments during the COVID-19 pandemic (7, 54, 70). To respond to the rapidity of COVID-19 spread worldwide, all of these societies produced interim guidelines without the usual rigorous protocol review. Now, this review provides such societies the evidence-based data needed to refine their guidelines.

To address the questions of gamete donor eligibility during this pandemic, the FDA has determined that since “respiratory viruses, in general, are not known to be transmitted by implantation, transplantation, infusion, or transfer of human cells, tissues, or cellular or tissue-based products” and “there have been no reported cases of transmission of COVID-19 via human cells, tissues, or cellular or tissue-based products,” the current guidelines remain unchanged (28). Additionally, at this time, the FDA does not even recommend screening blood donor candidates for SARS-CoV-2 (28). Individuals in the acute phase of the disease may benefit from specific precautions to avoid sexual intercourse for 2–4 weeks, but the universal precautions already practiced worldwide to prevent the transmission of all infectious diseases are likely adequate and sufficient to prevent viral transmission. This systematic review is in concordance with these guidelines and concludes that COVID-19 is not an STD.

## CONCLUSION

On the basis of the current international scientific data, and unless new conclusive data will be published, it is concluded that COVID-19 may affect male fertility but it is not an STD. This information is important for clinicians, guidelines for public health recommendations, FDA guidelines for gamete and tissue donor eligibility, and fertility treatments. Universal precautions practiced in clinical settings and laboratories to prevent the transmission of known or unknown viral infections are adequate and sufficient at this time. We suggest that the recovered patients of COVID-19, especially those with infertility, should be evaluated and followed-up for their ovarian and testicular function.

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