Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Sperm quality and absence of SARS-CoV-2 RNA in semen after COVID-19 infection: a prospective, observational study and validation of the SpermCOVID test

Gilbert G. G. Donders, M.D., Ph.D.,[a,b,c] Eugene Bosmans, Pharm.D.,[d,e] Jente Reumers, M.Sc, R.N.,[b] Francesca Donders, M.D.,[b] Jef Jonckheere, Pharm.D.,[d,f] Geert Salembier, Pharm.D.,[d,f] Nora Stern, M.D.,[g] Yves Jacquemyn, M.D., Ph.D.,[a] Willem Ombelet, M.D., Ph.D.,[h] and Christophe E. Depuydt, M.Sc., Ph.D.[d,e]

[a] University Hospital Antwerpen, Antwerp, Belgium; [b] Femicare, Clinical Research for Women, Tienen, Belgium; [c] Department of Obstetrics and Gynecology, Regional Hospital Heilig Hart, Tienen, Belgium; [d] Department of Hormonology and Reproductive Health, Algemeen Medisch Laboratorium (AML), [e] Department of Clinical and Molecular Pathology, and [f] Department of Clinical Microbiology, AML, Sonic Healthcare, Antwerp, Belgium; [g] Hôpital Universitaire Des Enfants Reine Fabiola, Brussels, Belgium; and [h] Genk Institute for Fertility Technology, Ziekenhuis Oost-Limburg (ZOL) Hospitals, Genk, Belgium

Objective: To study the contagiousness of sperm and its influence on fertility after recovery from COVID-19 infection.
Design: Prospective cohort study.
Setting: University medical center.
Patient(s): One hundred twenty Belgian men who had recovered from proven COVID-19 infection.
Intervention(s): No intervention was performed.
Main outcome measure(s): Semen quality was assessed using the World Health Organisation criteria. DNA damage to sperm cells was assessed by quantifying the DNA fragmentation index and the high density stainability. Finally antibodies against SARS-CoV2 spike-1 antigen, nuclear and S1-receptor binding domain were measured by Elisa and chemilumenscent microparticle immunoassays, respectively.
Result(s): SARS-CoV-2 RNA was not detected in semen during the period shortly after infection nor at a later time. Mean progressive motility was reduced in 60% of men tested shortly (<1 month) after COVID-19 infection, 37% of men tested 1 to 2 months after COVID-19 infection, and 28% of men tested >2 months after COVID-19 infection. Mean sperm count was reduced in 37% of men tested shortly (<1 month) after COVID-19 infection, 29% of men tested 1 to 2 months after COVID-19 infection, and 6% of men tested >2 months after COVID-19 infection. The severity of COVID-19 infection and the presence of fever were not correlated with sperm characteristics, but there were strong correlations between sperm abnormalities and the titers of SARS-CoV-2 IgG antibody against spike 1 and the receptor- binding domain of spike 1, but not against nucleotide, in serum. High levels of antisperm antibodies developed in three men (2.5%).
Conclusion(s): Semen is not infectious with SARS-CoV-2 at 1 week or more after COVID-19 infection (mean, 53 days). However, couples with a desire for pregnancy should be warned that sperm quality after COVID-19 infection can be suboptimal. The estimated recovery time is 3 months, but further follow-up studies are under way to confirm this and to determine if permanent damage occurred in a minority of men. (Fertil Steril® 2022;117:287–96. ©2021 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: DNA fragmentation index, infertility, real-time quantitative PCR, test validation, transmission risk

DIALOG: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/33471

Received July 10, 2021; revised October 24, 2021; accepted October 26, 2021; published online December 20, 2021.
Supported in part by Femicare Vereniging zonder Winstoogmerk (VZW) and AML (R20-014). AML and Femicare financed the testing and patient expenses. None of the investigators received any remuneration.
G.G.G.D. has nothing to disclose. E.B. has nothing to disclose. J.R. has nothing to disclose. F.D. has nothing to disclose. J.J. has nothing to disclose. G.S. has nothing to disclose. N.S. has nothing to disclose. Y.J. has nothing to disclose. W.O. has nothing to disclose. C.E.D. has nothing to disclose.
Reprint requests: Gilbert G. G. Donders, M.D., Ph.D., Department of Obstetrics and Gynecology, Division of Infectious Diseases and Lower Genital Tract Diseases, Drie Eycken straat 1, 2000 Antwerpen-Ekeren, Belgium (E-mail: gilbert.donders@uza.be).

Fertility and Sterility® Vol. 117, No. 2, February 2022 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2021.10.022

COVID-19 (corona virus disease first discovered in 2019), caused by the SARS-CoV-2 virus (severe acute respiratory syndrome by corona virus type 2), was recognized as a worldwide pandemic on March 11, 2020 (1). One year later (April 2021), 949,996 people in Belgium, with a population of 11 million, tested positive for SARS-CoV-2, and 23,747 people died from COVID-19 (https://epistat.wiv-isp.be/covid/), indicating the potential severity and pathogenicity of this viral infection.

SARS-CoV-2 infects human cells by binding the spike glycoprotein to angiotensin-converting enzyme 2 (ACE-2) (2). Infection is mediated by interaction of the SARS-CoV-2 receptor-binding domain (RBD) (3) of the spike protein with the ACE2 viral receptor on host cells (4).The male reproductive system has been hypothesized to be a potential target for SARS-CoV-2, since testicular cells on both sides of the blood–testis barrier not only express the ACE2 receptor (5), but also possess the entire repertoire of receptors (ATR1, ATR2, MAS), TMPRS2 (if expressed on testicle cells), and ligand-processing enzymes (ACE1 and ACE2) needed to support the angiotensin signaling cascade (6, 7). Furthermore, because other RNA viruses, such as Zika, Ebola, and Marburg viruses, are able to cross the blood–testis barrier and can cause local inflammation (2, 8–10), it was our aim to determine whether SARS-CoV-2 could cross the blood–testis barrier and be detected in human semen after COVID-19 infection and negatively affect sperm parameters and fertility, since there is still considerable uncertainty about this question despite several prior studies addressing it. For this purpose, we validated a SARS-CoV-2 RNA test system for detection in semen (SpermCOVID test). Because previous studies reported that the testes of COVID-19 patients exhibited significant seminiferous tubular injury, reduced Leydig cells, and mild lymphocytic inflammation (11), we also assessed the presence and quantity of SARS-CoV-2 antibody titer in serum and semen after COVID-19 infection to test the immunologic involvement in reduced sperm quality.

MATERIALS AND METHODS

Objectives

The purpose of this prospective, observational trial was to determine if SARS-CoV-2 could be detected in semen of adult men who had recovered from COVID-19 infection. In addition, this study assessed the influence of COVID-19 on fertility parameters and DNA damage in semen. Finally, we wanted to assess the immunologic etiology of abnormal sperm parameters by correlating them with anti-SARS-CoV-2 antibody responses in blood and semen.

Patients and Sampling Methods

Male patients presenting with a positive SARS-CoV-2 test result in our laboratory were notified of our prospective study and invited to participate by contacting them by mail or telephone. Men between the ages of 18 and 70 years who had suffered a proven COVID-19 infection and were asked to provide semen and blood samples and to fill out a questionnaire inquiring about their living conditions and the characteristics of the COVID-19 disease they had experienced. Semen samples were tested according to World Health Organization (WHO) recommendations (12).

The trial was approved by the ethical committee of University Hospital Antwerp on May 11, 2020 (B3002020000078). The trial was conducted in compliance with the principles of the Declaration of Helsinki (2008) and the principles of Good Clinical Practice and in accordance with regulatory requirements.

Men were eligible to participate in the study if they tested positive on a nasopharyngeal SARS-CoV-2 real-time (RT)-polymerase chain reaction (PCR) swab at a minimum of 1 week and a maximum of 6 months before inclusion. Men who had suffered symptoms of COVID-19 and subsequently tested positive for serum SARS-CoV-2 antibodies were also eligible. Participants had to be free of major symptoms for at least a week at inclusion. After the men had completed an internet-based or printed questionnaire inquiring about epidemiology and the characteristics of the COVID-19 disease, a sperm sample obtained by masturbation and a blood sample were taken at our center. From one to three follow-up visits were offered if the sperm tests were not normal. Participants who did not have proven post-SARS-CoV-2 infection or who were not able or willing to provide a semen sample were excluded from the analysis (Supplemental Fig. 1, available online). Participants who had had a vasectomy were tested for serum antibodies and the SARS-CoV-2 PCR in semen but were excluded from the analysis of semen quality parameters.

The influence of COVID-19 disease severity on sperm quality was assessed by comparing individuals who experienced fever with those who did not, who were hospitalized with those who were not, and who were still suffering symptoms with those who were not. Because no single COVID-19 symptom, including fever, seemed to be associated with reduced sperm quality, we created a total symptom score by adding the number of symptoms each patient had during the acute episode of COVID-19 disease. This global symptom score was composed by calculating the number of different symptoms, resulting in a total symptom score between 0 (no symptoms) and 15 (maximal symptoms). The 15 symptoms listed were fever, cough, shortness of breath, fatigue, nasal congestion, headache, gastrointestinal symptoms (nausea, vomiting, diarrhea), chest pain, muscle pain, eye pain, throat pain, cerebral symptoms (dizziness, hallucinations, concentration problems), shaking (without fever), flu-like feelings, and other symptoms. The time lapse between the onset of infection and inclusion in the study was calculated as the time between a positive PCR test (or onset of symptoms) and the time of inclusion and was classified as 31 days or less (1 month), between 32 and 62 days (2 months), or between 63 days (2 months) and 181 days (6 months).

Because the proportion of PCR positivity in semen was expected to be low but was unknown at that moment, we decided to include semen samples from 100 participants. With an expected dropout rate of 20%, we aimed for 120 inclusions. Because the study was performed during the first and second waves of COVID-19 infection in Europe, none of the men were vaccinated against COVID-19.

Laboratory Procedures

Analysis of semen quality parameters. All sperm samples were analyzed following the WHO guidelines for semen analysis (12). Two to five days of sexual abstinence were asked of the participants before sperm samples were collected by masturbation into noncytotoxic sterile containers that were provided to them by the study center. Sperm was transported to the laboratory while being kept at body temperature and analyzed immediately on arrival in the laboratory. Four hours was the maximum time lapse allowed for the results of motility testing. The following parameters were measured in all semen samples: volume (mL), sperm concentration (10^6/mL), total number of spermatozoa per ejaculate, total motile count, morphology, pH, and presence of round cells (10^6/mL).

Antisperm antibodies in semen. Antisperm antibodies (ASA) in semen were detected with the spermMar test kit for IgG and IgA (FertiPro, Beernem, Belgium). When enough spermatozoa with grade A motility were present, direct IgA and IgG mixed antiglobulin reaction (MAR) tests were performed. Light microscopy was used to determine the percentage of motile spermatozoa with attached latex particles. The location on the spermatozoan (head, midpiece, tail) where the latex particles attached was also recorded. The diagnosis of immunologic infertility is suspected when 10% to 39% of motile spermatozoa are attached to latex particles; if 40% or more of the spermatozoa are attached, immunologic infertility is highly probable.

Sperm chromatin structure assay. The flow cytometric sperm chromatin structure assay was performed as previously described (13). The assay measures the percentage of spermatozoa with fragmented DNA (DNA fragmentation index, DFI) as well as the percentage of spermatozoa with high DNA stainability (HDS). An HDS value below 7.5% was considered normal, a value between 7.5% and 15% was considered elevated, and a value above 15% was considered abnormal. A DFI value between 15% and 25% was considered elevated, and a DFI value above 25% was considered abnormal.

Validation of SpermCOVID test: detection of SARS-CoV-2 RNA in sperm. The PerkinElmer SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) assay is CE-IVD marked and intended for in vitro diagnostic use in Europe. It is intended for the qualitative detection of nucleic acid from the SARS-CoV-2 virus in human oropharyngeal swab, nasopharyngeal swab, and saliva specimens collected by healthcare providers from individuals suspected of having COVID-19 or asymptomatic carriers.

We used the Chemagic Viral DNA/RNA 300 Kit H96 (Chemagen, PerkinElmer; cat no. CMG-1033-S, Zaventem, Belgium) for automated isolation from 300 μL of semen using the Chemagic 360 instrument. After viral RNA was isolated using the short protocol, the eluted viral RNA was subsequently converted to cDNA with the TaqPath COVID-19 CE-IVD RT-PCR Kit (ThermoFisher Scientific, Waltham, MA). The PerkinElmer SARS-CoV-2 Real-time RT-PCR assay was used to simultaneously detect two SARS-CoV-2 target genes (N-gene and ORF1ab-gene), an internal control gene (MS2-phage), and a human RNA control using Quantstudio 7 flex (Applied Biosystems, Waltham, MA).

For the N- and ORF1ab-genes, a threshold value of less than 40 cycles was defined as positive for SARS-CoV-2, and a value of 40 cycles or more was defined as a negative test. The limit of detection is 2 copies/μL. The internal control and human RNA control were positive for all tested semen samples. SARS-CoV-2–positive culture medium from nasal swabs was used to spike five different semen samples to validate the entire SARS-CoV-2 detection protocol.

Detection of SARS-CoV-2 IgG antibodies in serum. To assess the level of immunity against COVID-19, a blood sample was collected at the moment of semen sampling to test serum IgG. Three different serologic tests were performed, since SARS-CoV-2 RNA encodes for four structural proteins: spike (S, two subunits S1 and S2), membrane (M), envelope (E), and nucleocapsid (N) (4, 14). The RBD is included within the S1 subunit and has a high affinity for the ACE2 receptor on the cell surface membrane.

Qualitative detection of IgG antibodies to the nucleocapsid protein (N) of SARS-CoV-2 (sIgG-N) was performed by a chemiluminescent microparticle immunoassay intended for the qualitative detection of IgG antibodies to the nucleocapsid protein of SARS-CoV-2 in human serum (SARS-CoV-2 IgG for use with ARCHITECT; Abbott Laboratories, Abbott Park, Illinois; reference 06R8620). Briefly, the amount of IgG antibodies was determined by comparing its chemiluminescent relative light unit with the calibrator relative light unit (index S/C). Using an index S/C threshold of 1.4 for positivity, the manufacturer reported a sensitivity of 86.4% after 7 days from symptom onset and 100% after 14 days, and a specificity of 99.6%, using RT-PCR as the gold standard.

Semiquantitative in vitro determination of IgG antibodies to the S1 domain of the spike protein of SARS-CoV-2 (sIgG-S) was done with the use of the anti-SARS-CoV-2 IgG enzyme-linked immunosorbent assay of Euroimmun (Lübeck, Germany) in batches according to the manufacturer's instruction. The semiquantitative ratio was calculated by dividing the extinction of the control or patient sample by the extinction of the calibrator. A ratio <0.8 was interpreted as negative, a ratio ≥ 0.8 to <1.1 as borderline, and a ratio ≥ 1.1 as positive.

For qualitative and semiquantitative detection of IgG neutralizing antibodies to the RBD of the S1 subunit of the spike protein of SARS-CoV-2 (sIgG-RBD), we used the AdviseDx SARS-CoV-2 IgG II assay on the ARCHITECT i System (Abbott Laboratories, reference 6S60-30) to measure the amount of neutralizing antibodies present in serum. The AdviseDx SARS-CoV-2 IgG II assay is a chemiluminescent microparticle immunoassay that detects the amount of neutralizing RBD IgG antibodies to SARS-CoV-2 in serum from individuals who are suspected to have had COVID-19 disease or in serum and plasma of individuals who may have been infected by SARS-CoV-2. The result unit for the AdviseDx SARS-CoV-2 IgG II assay is AU/mL, and the threshold for positivity is 50.0 AU/mL. Samples with a SARS-CoV-2 IgG value exceeding 40,000.0

AU/mL were manually diluted (1:2) according to the manufacturer's instructions with ARCHITECT Multi-Assay Manual Diluent.

Statistical Analysis

The analysis of the total number of sperm cells in a sample included only the samples for which the participant had reported on the questionnaire that a complete sample was collected. For analysis of discrete variables according to the WHO criteria, the χ^2 test was used, except when numbers below 5 were encountered in one or more of the computed cells, in which case Fisher's exact test was used. For normally distributed data, ANOVA was used to compare means of groups, and for correlation of continuous variables, Spearman rho analysis was used. Linear multiple regression analysis was performed after testing for collinearity of the variables used in the model. Collinearity was tested by calculating the variance of inflation factor (VIF); VIF <5.0 indicates absence of collinearity. Excel 2017 was used for data collection and management, and SPSS 27.0 was used for statistics. $P \leq .05$ was considered to indicate statistical significance.

RESULTS

Patient Characteristics after COVID-19 Infection

Of the 123 men who presented, 1 refused to provide informed consent, 2 tested negative on SARS-CoV-2 RNA PCR and antibodies, despite symptoms suggestive of COVID-19, and 1 was excluded due to negative antibody testing after a symptomatic episode suggestive of COVID-19, but without confirmed positive SARS-CoV-RNA PCR. The remaining 120 participants who had recovered from a proven COVID-19 infection were included in the study. Their mean age was 34.7± 9.1 years (range, 18–69 years), and their mean body mass index (BMI) was 24.7 ± 4.4 kg/m^2. 11 (9.2%) fitting the diagnosis of obesity (BMI>30) (Table 1). Sixteen participants (13.3%) had other underlying medical conditions putting them at higher risk for severe symptoms of COVID-19, such as chronic lung disease, cardiovascular disease, diabetes, and decreased immunity. The majority of the participants had no children (59.2%); 8 participants (6.7%) reported having had fertility problems before inclusion.

All but one participant tested positive for COVID-19 with an official SARS-CoV-2 PCR test performed in a nationally approved laboratory. One participant (0.8%) could not be PCR tested for COVID-19 because of regulatory issues, but he suffered from COVID-19 symptoms and subsequently tested positive for anti-SARS-CoV-2 IgG in his serum and was included in the study. All included participants reported COVID-19 symptoms during their active infection period (Table 1). Half of the participants (50.0%) had four or five symptoms during the initial infection, 26.3% had fewer than four symptoms, and 23.7% had more than five symptoms. The most frequently reported symptoms were fatigue (78.3%), loss of smell and taste (65%), headache (60%), cough (59.1%), and fever of 38°C and above (35.8%). Most participants (95.8%) recovered from COVID-19 at home. Five participants (4.2%) had to be hospitalized, two in an intensive care unit and one in need of mechanical ventilation.

Contagiousness of Semen after SARS-CoV-2 Infection

SARS-CoV-2 RNA was detected in none of the 120 collected semen samples with the validated SpermCOVID PCR test at a mean of 52.7 ± 35.1 days after COVID-19 infection.

Quality Parameters of Semen after SARS-CoV-2 Infection

Of the 120 participants, 2 vasectomized participants were excluded for analysis of semen quality parameters. The

TABLE 1

Epidemiologic characteristics of different groups based on time frame of positive nasopharyngeal swab for SARS-CoV-2 RNA until inclusion in trial.

	Time lapse since COVID infection			
Characteristic	**Short 0–31 days**	**Intermediate 32–62 days**	**Long 63 (+) days**	**Total 0–181 days**
No. of participants	35	51	34	120
No. of days postinfection	21.5 ± 7.1	45.3 ± 8.3	99.1 ± 34.3	53.6 ± 36.0
Age (y)	36.5 ± 1.2	32.7 ± 7.5	35.8 ± 9.7	34.7 ± 9.1
Body mass index (kg/m^2)	24.4 ± 5.1	24.4 ± 4.2	25.4 ± 4.0	24.7 ± 4.4
Having children	17 (48.6%)	17 (33.3%)	16 (47.1%)	49 (4.8%)
Reported infertility	3 (8.6%)	3 (5.9%)	2 (5.9%)	8 (6.7%)
Current smoking	3 (8.6%)	6 (11.8%)	0 (0%)	9 (7.5%)
Positive SARS-CoV-2 PCR nasopharyngeal swab	35 (100%)	51 (100%)	33 (97.1%)	119 (99.2%)
Underlying conditions	6 (17.1%)	5 (9.8%)	5 (14.7%)	16 (13.3%)
Total symptom score (0–15)	4 ± 1.4	5 ± 1.8	4 ± 1.4	5 ± 1.6
Still having COVID–19 symptoms at inclusion	18 (51.4%)	14 (27.5%)	9 (26.5%)	37 (3.8%)
Fever (>38°C)	10 (28.6%)	22 (43.1%)	11 (32.4%)	43 (35.8%)
Home recovery	34 (97.1%)	49 (96.1%)	32 (94.1%)	115 (95.8%)
Hospitalization	1 (2.9%)	2 (3.9%)	2 (5.9%)	5 (4.2%)

Note: Data are shown as number (percentage of total) or mean ± SD.

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remaining 118 samples were analyzed at a mean of 54 days after SARS-CoV-2 infection: 30% (n = 36) within 1 month after their positive PCR test ("short time lapse" group), 42.5% (n = 51) between 1 and 2 months after their positive PCR test ("intermediate time lapse" group), and 29% (n = 34) 2 months or more after their positive PCR test ("long time lapse" group). Of all sperm samples, 63% (76/120) were analyzed in the laboratory within 1 hour and 89% (n = 107) within 4 hours after production. All 118 samples were used for analysis of volume (mL), sperm concentration (10^6/mL), total number of spermatozoa per ejaculate, pH, and presence of round cells (10^6/mL). For the analysis of total motile cell count and the number of progressive spermatozoa per ejaculate, we restricted the time interval between production and analysis to 240 minutes (n = 107).

One quarter (25.4%; 30/118) of all examined men after SARS-CoV-2 infection were oligozoospermic; 44.1% (52/118) had asthenozoospermia; and two thirds (67.0%; 79/118) had teratozoospermia. Sperm morphology was more affected than sperm motility after SARS-CoV-2 infection, whereas sperm concentration was least affected ($P<.0001$). Only 24.6% (29/118) of participants had fully normal sperm parameters (concentration, motility, and morphology). About one third (38/118) had asthenozoospermia (n = 10) or teratozoospermia (n = 28); 25.4% (30/118) had two abnormal semen parameters (9 oligozoospermia and teratozoospermia; 21 asthenozoospermia and teratozoospermia); and 17.8% (21/118) had three (oligozoospermia, asthenozoospermia, and teratozoospermia).

Clinical parameters or comorbidities recognized as risk factors for severe COVID-19 infection, such as age, BMI, and smoking, did not seem to interfere with most of the sperm quality parameters, except that age was correlated with a higher DFI and a lower density (percentage with HDS). Severity of infection (i.e., the need to be hospitalized) was associated with a lower motility and morphology score ($P=.03$), but having had fever and total symptom score had no effect on sperm quality (Table 2).

Categorizing the data according to short (< 1 month), intermediate (1–2 months), or long (>2 to maximum 6 months) time lapse after COVID-19 infection revealed some striking abnormalities of sperm characteristics according to the WHO criteria. Sperm count less than 15 million/mL was six times more frequent in men tested within 1 month after SARS-CoV-2 infection (n = 15, 37%) than in men tested after 2 months (6.3%) ($P=.003$) (Table 2). We also found a much higher number of men with less than 32% progressive spermatozoids within the first month after COVID-19 infection (21/35, 60%), than between 1 and 2 months and more than 2 months after COVID-19 infection: 16/43 (37%) and 8/29 (28%), respectively ($P=.02$). Similarly, total motility decreased to less than 40% in 18/35 (51%) of men early after infection, compared with 11/43 (26%) between 1 and 2 months and 6/29 (21%) after 2 months ($P=.01$). Of note, morphology does not seem to be affected by time lapse after COVID-19 infection. There was a trend toward decreasing MAR IgG and increasing MAR IgA with increasing time lag after COVID-19 infection.

Signs of DNA damage of spermatozoa were most pronounced within the first month after COVID-19 infection. A DFI greater than 25% (abnormal) was found in 10 (29%) early samples as compared with 6 (11%) and 5 (15%) samples after 1 month and more than 2 months, respectively ($P=.049$). Equally, mean HDS was higher in the group with short time lapse (19%) than in the groups with intermediate (16%) and long time lapse since infection (13%) ($P=.036$).

In regression analysis, examination time at less than 1 month after COVID-19 infection was associated with reduced sperm motility ($P=.01$), but also with reduced total number of sperm cells and sperm cell concentration per milliliter ($P=.01$) (Table 3). The titer of antispike 1 and anti-S1-RBD serum IgG antibodies correlated reciprocally with both motility ($P=.04$) and sperm cell count ($P=.008$).

Multiple regression analysis was appropriate for all variables included. Age, BMI, COVID-19 disease severity, time

TABLE 2

Sperm quality in relation to timing after COVID-19 infection.

		Time lapse since COVID infection			
Characteristic	**Short 0–31 days**	**Intermediate 32–62 days**	**Long 63 (+) days**	**Total 0–181 days**	***P* value**
No. of participants	35	51	32[a]	118[a]	
Sperm concentration <15 million/mL	13 (37.1%)	15 (29.4%)	2 (6.3%)	30 (25.4%)	.003
Total no. of sperm/ejaculate[b]	82.8 ± 109.0	98.4 ± 113.6	131.4 ± 9.1	101.6 ± 8.0	
Progressive motility <32%[c]	21 (60%)	16/43 (37.2%)	8/29 (27.6%)	45/107 (42.1%)	.02
Total motile count <40%[c]	18 (51.4%)	11/43 (25.6%)	6/29 (2.7%)	35/107 (32.7%)	.01
Morphology ideal shape <4%	27 (77.1%)	38 (74.5%)	25 (78.1%)	90 (76.3%)	
MAR IgG >10%	1/33 (3.0%)[d]	3/50 (6.0%)	0/31 (.0%)	4/114 (3.5%)	
MAR IgA >10%	3/30 (1.0%)[d]	5/45 (11.1%)	7/31 (22.6%)	15/106 (14.2%)	
HDS >15%	2 (5.7%)	6 (11.8%)	0	8 (6.8%)	
DFI >25%	10 (28.6%)	6 (11%)	5 (15.6%)	(17.8%)	.049
SARS-CoV-2 RNA in semen	0 (.0%)	0 (.0%)	0 (.0%)	0 (.0%)	

Note: DFI = DNA fragmentation index; HDS = high DNA stainability; MAR = mixed erythrocyte-spermatozoa antiglobulin reaction.
[a] Semen quality parameters were analyzed in 118 semen samples (2 excluded due to vasectomy).
[b] Total number of sperm/ejaculate was analyzed on semen samples that subjects could fully collect (no semen was lost).
[c] Mobility parameters ware analyzed on semen samples that were analyzed in the laboratory within 4 hours after semen production.
[d] In one case, MAR IgG and MAR IgA were >40%, indicating immunologic infertility.

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TABLE 3

Spearman rho correlation of sperm quality parameters in relation to clinical characteristics and immunity parameters of participants in the SpermCOVID study.

		Risk factor																			
		Age		BMI		Smoking		Time lapse period		Symptom score		Severity		sIgG-RBD		sIgG-N		sIgG-S1			
Sperm quality	n	r^2	*P*	r^2	*P*	r^2	*P*	r^2	*P*	r^2	*P*	r^2	*P*	r^2	*P*	r^2	*P*	r^2	*P*		
Volume	118	−.238	.009	−.111	.2	.065	.5	.019	.8	.001	1	−.04	.7	.131	.6	.064	.5	.107	.3		
pH	118	−.01	.9	−.007	.9	−.059	.5	−.1	.3	−.025	.8	−.041	.7	.218	.018	.155	.11	.204	.028		
Total no. of sperm cells	118	−.097	.4	−.094	.4	.072	.5	.26	.009	−.047	.6	−.101	.3	−.17	.09	−.168	.11	−.157	.12		
Sperm concentration	118	−.091	.3	−.004	1	.074	.4	.257	.005	−.034	.7	−.101	.3	−.259	.005	−.253	.008	−.25	.007		
Total mobility count	118	−.164	.076	.061	.5	−.055	.6	.247	.007	−.032	.7	−.196	.033	−.234	.011	−.185	.56	−.188	.043		
Progressive mobility	118	−.194	.035	.106	.3	−.029	.8	.252	.006	−.087	.3	−.206	.025	−.236	.011	−.214	.27	−.185	.045		
% ideal forms	118	−.15	.11	.023	.8	−.072	.4	.094	.3	−.05	.6	−.195	.034	−.177	.057	−.152	.12	−.161	.083		
OAT severity	118	.123	.2	.68	.5	.084	.4	−.226	.014	.078	.4	1	.28	.287	.002	.26	.005	.314	.001		
MAR IgG	114	−.009	.9	.011	.9	−.133	.16	.138	.014	−.056	.6	−.059	.5	.148	.12	.004	1	.151	.11		
MAR IgA	106	.016	.9	−.112	.3	.042	.7	.11	.014	−.066	.5	−.025	.8	.055	.6	−.126	.2	−1.06	.28		
HDS	118	−.185	.044	−.145	.12	−.07	.4	−.195	.014	−.132	.45	.126	.2	.21	.021	.064	.5	.21	.023		
DFI	118	.218	.018	.073	.4	−.035	.7	−.032	.014	−.006	1	.179	.052	.34	.0001	.108	.3	.289	.002		

Note: BMI = body mass index; DFI = DNA fragmentation index; HDS = high DNA stainability; MAR = mixed erythrocyte-spermatozoa antiglobulin reaction; OAT = oligo-astheno-teratozoospermia; sIgG-N = serum immune globulin G (sIgG) aginst the nucleotide; sIgG-RBD = sIgG aginst the receptor domain of S1; sIgG-S1 = SIgG against the antigen S1.

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lapse after COVID-19, and antispike 1 SARS-CoV-2 antibody all showed VIFs less than 1.2 (Table 4). Sperm motility was affected by age ($P<.005$), time lapse after COVID-19 ($P<.004$), and anti-S1 SARS-CoV-2 IgG antibodies ($P<.005$). Reduced sperm concentration was correlated with the time lapse after COVID-19 ($P=.048$) and anti-S1 SARS-CoV-2 IgG antibodies ($P=.034$). In addition, DFI and HDS were correlated with age and anti-S1 SARS-CoV-2 IgG antibodies, and HDS was also inversely related to increased time lapse after COVID-19 and COVID symptoms ($P=.02$). Smoking, BMI, and severity of COVID-19 disease (admission to hospital) were not associated with any of the sperm quality parameters.

Antisperm Antibodies in Semen

Enough motile spermatozoa were present in 106 participants to perform both the IgA and the IgG direct MAR test. An overview is given in Supplemental Table 1. In 61% of semen samples (65/106), IgA ASA were detected, mainly localized to the tail of the spermatozoa. In one participant, the percentage of IgA ASA-positive spermatozoa was above 40%, indicating immunologic infertility (1/106; 0.9%), whereas in 14 subjects, the percentage of IgA ASA-positive spermatozoa was between 10% and 40% (13.2%, reduced fertility). IgG ASA were less frequently detected than IgA ASA after COVID-19 (34/106; 32.1%) ($P<.0001$). In two subjects, more than 90% of motile spermatozoa had IgG ASA that were bound to the entire spermatozoan. Both participants fathered young children (<2 years old) before they became COVID-19 infected. Both IgA and IgG ASA were detected in 25 subjects (23.6%), IgA ASA without IgG ASA was detected in 40 subjects (37.7%), IgG ASA without IgA ASA was detected in 9 subjects (8.5%), and neither IgA nor IgA ASA were detected in 32 subjects (30.2%) (Supplemental Table 1).

Serum SARS-CoV-2 Immunity Testing

COVID-19 immunity. One hundred six of 120 participants (88.3%) tested positive for SARS-CoV-2 IgG serum nucleocapsid antibodies (sIgG-N). One hundred fourteen of 119 (95.8%) tested positive for the neutralizing IgG antibodies against the spike 1 RBD of SARS-CoV-2 (sIgG-RBD).

Antibody titers and sperm quality. Sperm concentration and motility decreased with increasing serum antibody titers, whereas DNA damage (high density score and DFI) increased (Table 2). In addition, the global OAT (oligo-astheno-teratozoospermia) severity score was strongly correlated with increasing antibody levels.

DISCUSSION

SARS-CoV-2 uses the ACE-2 receptor to infiltrate human cells. These receptors are found in the respiratory tract where the infection mostly occurs, but also in the male reproductive tract (2). In analogy with other RNA viruses that cause viremia and cross the blood–testis barrier, we hypothesized that the presence of SARS-CoV-2 RNA in human semen could lead to transfer of this virus through sexual intercourse. We validated a PCR test (SpermCOVID test) especially to test this

TABLE 4

Multivariate linear regression analysis testing mean sperm progressive motility, mean sperm concentration, DNA stability (fragmentation index and high DNA stability percentage) and MAR test against different variables related to the past COVID-19 infection patients have experienced.

Sperm characteristics		Progressive motility (%)		Concentration ($\times 10^6$/mL)		DFI		HDS		MAR direct IgG	
Variables included in model	VIF	t	*P* value	t	*P* value	t	*P* value	t	*P* value	t	*P* value
BMI	1.154	1.07	.29	−.46	.65	1.86	.07	.15	.88	1.17	.25
Current smoking	1.084	−.55	.58	1.30	.20	.40	.69	−.98	.33	−.80	.43
Age	1.204	−2.87	.005	−.11	.92	3.98	.000	−3.12	.002	−.59	.56
Time lapse since COVID–19	1.039	2.92	.004	2.00	.048	−1.51	.14	−2.32	.022	.10	.92
Total symptom score	1.166	−1.18	.24	.06	.95	.03	.98	−2.33	.022	−.69	.49
COVID–19 severity	1.410	−.35	.73	−.33	.74	−.13	.90	1.53	.13	−.35	.73
Serum antispike–1 IgG	1.224	−2.83	.005	−2.15	.034	3.54	.001	2.21	.029	−.77	.45

Note: VIFs of all variables were between 1.1 and 1.4, indicating absence of collinearity (VIF < 5). DFI = DNA fragmentation index; HDS = high DNA stability; MAR = mixed erythrocyte- spermatozoa antiglobulin reaction; VIF= variance of inflation factor.

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hypothesis. However, we could not detect any SARS-CoV-2 RNA during convalescence after documented COVID-19 infection from testing an average 53 days after a positive SARS-CoV-2 nasopharyngeal PCR test. Tests were negative as late as 181 days and as early as 6 days after positive testing. This is an important finding, since whether SARS-CoV-2 could be transmitted sexually after convalescence from COVID-19 infection was still unclear. These findings are similar to the findings of Pan et al., who also could not detect any SARS-CoV-2 RNA in human semen at an average of 31 days after acute COVID-19 infection (15), and of Holtmann et al. (2), who reported negative sperm RNA results in 28 men tested 8 to 54 days after (Supplemental Figure 1) COVID-19 infection.

Our data confirm the findings of a smaller trial by Holtmann et al. (2), which also detected no SARS-CoV-2 RNA in human semen obtained 8 to 54 days after the absence of symptoms, a period similar to our short and medium-long postinfection lapse time groups. In one study in which SARS-CoV-2 RNA was detected in 6 of 32 semen samples, 4 of these 6 participants suffered from a severe, active COVID-19 infection while the sperm was being tested (5). In concordance with this, viral SARS-CoV-2 RNA was also encountered in testicular cells and Leydig cells of two men who died from COVID-19 (16). According to our and Holtmann's data, however, SARS-CoV-2 RNA rapidly disappears from the testes after recovery from COVID-19 infection in all men (2). Therefore, it is conceivable that the blood–testis barrier can be crossed by the SARS-CoV-2 virus during the acute phase of the disease, but not after convalescence (21 days).

Still, despite the absence of detection of SARS-CoV-2 RNA in semen, we found evidence of severely decreased quality parameters after convalescence from SARS-CoV-2 infection. The negative impact of COVID-19 on sperm quality mainly affected sperm concentration, motility, and DFI, whereas the correlation with abnormal morphology was less clear. These results confirmed data from Holtmann et al. (2), who also found mainly decreased concentration and motility of spermatozoa in men who had had moderate COVID-19 infection (2). In that study, such abnormalities were not found in men with mild COVID-19 infection or in COVID-19-negative controls. In contrast, in our study we found no differences in sperm quality parameters between patients who had to be admitted to the hospital and those who could stay home with COVID-19 infection and no correlations between sperm quality parameters and total COVID-19 symptom score.

The decrease in sperm quality parameters was greatest in men who were tested soon after recovery from COVID-19, less in men tested after 1 month, and least in men tested after 2 months or more. This could lead to the conclusion that the temporary sperm abnormalities seen during acute COVID-19 infection could be due to fever, since hyperthermia is known to have this effect (17). During other viral infections, such as influenza, sperm motility can be linked to the severity of fever, with a maximal decrease of motility seen at day 37 and normalization of motility by day 54 after fever (18). However, in our study, the presence and severity of fever and symptom score during COVID-19 disease were not correlated with sperm quality parameters, indicating that other

mechanisms than fever linked to COVID-19 infection could be involved in the pathogenesis of sperm damage.

To assess these other mechanisms in further detail, we tested the strength of the immune response by measuring antispike (sIgG-S), antinucleotide (sIgG-N), and neutralizing anti-S1-RBD antibodies (sIgG-RBD) against SARS-CoV-2 in serum, and compared these findings with sperm quality measures, as well as with the presence of IgG and IgA antisperm antibodies on spermatozoa (MAR test). A very strong correlation was found between the titer of anti-SARS-CoV-2- S1 (sIgG-S) and -RBD (sIgG-RBD) serum antibodies and all sperm quality parameters, including increased DFI and HDS. The latter two markers of DNA damage are strongly linked to reduced fertility, independent of the WHO sperm quality parameters, and were associated with a dramatic reduction in pregnancy success in patients treated with intrauterine insemination for infertility, when they were inseminated with human papillomavirus (HPV)-infected sperm (19). Whereas in the case of HPV infection, the pathogenetic mechanism is thought to be linked to direct binding of HPV virions to the syndecan-1 receptor localized on the head area of the spermatozoan, inducing sperm DNA damage, the most likely explanation of reduced sperm function after COVID-19 infection is due to the induction of cytokines after IgA secretion. The attachment of both IgA and IgG ASA to the tail of the spermatozoa points to a common epitope for both antibody types against SARS-CoV-2 virus. This could explain the strong association between both WHO sperm quality parameters and markers of DNA damage in sperm with the antibody titers after COVID-19 infection.

We also demonstrated that twice as many convalescent COVID-19 participants had IgA ASA in their semen than IgG ASA ($P<.0001$). This is not unexpected, since IgA is the principal antibody secreted as a first-line defense by mucosal surfaces of the respiratory, gastrointestinal, and genitourinary tracts on a viral or bacterial challenge (20). In contrast to the local production of IgA, IgG diffuses from the blood to the semen (21), and IgG must find its way into external secretions via receptor-independent paracellular diffusion, receptor-mediated transepithelial transport, and fluid-phase endocytosis, all of which are different from the mechanism by which IgA and IgM enter secretions (22). Because we measured ASA an average of 54 days after SARS-CoV-2 infection, the short-term impact of the measured IgA ASA on fertility seems low, with only one participant having more than 40% of motile spermatozoa affected by IgA ASA. In the long-term, follow-up will have to show what happens to the majority of subjects in whom we detected IgA ASA, since augmented or aberrant presence of IgA immune complexes can result in excessive neutrophil activation, potentially leading to chronic tissue damage in multiple inflammatory, or even autoimmune, diseases (23). Therefore, sperm IgA ASA may have an impact on fertility in the longer term, and long-term follow-up is warranted. For that reason, we prolonged the follow-up time for our study participants and will report on the long-term results of sperm quality and immune reactions in a separate article. ASA can recognize spermatic surface antigens that can interfere with sperm motility and transport through the female reproductive tract and inhibit capacitation and acrosome reaction (3), mediate the release of cytokines that affect sperm function, and impair sperm–cervical mucus interaction (24), induce sperm cytotoxicity, increase sperm phagocytosis, and inhibit embryo development and implantation. As a result, natural pregnancy rates decrease when ASA are present (24). The strong IgG ASA positivity against the entire spermatozoan soon after SARS-CoV-2 infection suggests there may have been a breach of the blood–testis barrier during the acute phase of COVID-19. This is in agreement with previous studies on a limited number of patients who were in the acute phase of COVID-19 at the moment of testing, who showed SARS-CoV-2 RT-PCR positivity in the semen (5).

The strong points of this study are the unbiased group of patients (not just men presenting with infertility problems), the large study group, the unequivocal proof of the evidence and timing of COVID-19 infection, and the possibility of studying both contagiousness and sperm quality parameters in association with disease severity and SARS-CoV-2 antibody production. Additionally, differences in the COVID-19 variants [the so-called British (α), South-African (β), Brazilian (γ), and Indian (δ) variants] had no effect on our outcome data, since our inclusion period occurred during the first and second COVID-19 waves, when only the original Chinese/Huwan variant was prevalent.

A weakness of our study is that we had no comparative sperm samples from the participants before they contracted COVID-19, nor were we able to include samples from matched control men without COVID-19, since the only comparison samples at our disposal were from infertility patients or from patients who were in general younger than our study patients. Still, by introducing a follow-up period of 6 months as an amendment to our study, we will be able to provide specific detailed information on the mechanisms of recovery of sperm quality over time.

CONCLUSION

In this large trial with 120 post-COVID-19 patients, using a newly validated SpermCOVID test, we provide strong evidence that the SARS-CoV-2 virus cannot be sexually transmitted through sperm after convalescence from COVID-19, since none of the semen samples contained viral RNA. On the other hand, we found profound reductions in sperm concentration, the number of spermatozoa produced, and both total and progressive motility of the spermatozoa after COVID-19 infection. Sperm quality parameters were most severely damaged when assessed during the first month after COVID-19 infection, were less pronounced in men tested more than 1 month after infection, and were almost normal two months or longer after infection. Unexpectedly, fever and the severity of COVID-19 symptoms were not associated with reduced sperm quality parameters. The titers of specific anti-SARS-CoV-2 IgG antibody against the spike and the spike-1-receptor-region-domain antigens of the virus, on the other hand, showed a very strong correlation with reduced sperm function, indicating an immunologic rather than a

fever-induced causality of the temporary sperm dysfunction. This was confirmed by a correlation of reduced sperm quality with increased antisperm IgA and IgG antibodies in the semen. Recovery times of the affected semen parameters are currently under investigation in a prolonged follow-up study.

AUTHORS' ROLES

Conception and design: G.G.G.D., E.B., F.D., W.O., and C.E.D. Acquisition of data: G.G.G.D., E.B., J.R., F.D., and C.E.D. Analysis and interpretation of data: G.G.G.D., J.R., and C.E.D. Drafting the manuscript: G.G.G.D., J.R., and C.E.D. Laboratory testing: E.B., C.E.D., J.J., and G.S. Critical revision of the manuscript: G.G.G.D., E.B., W.O., Y.J., C.E.D., S.N., and F.D. Final approval to be published: all authors. Agreement to be accountable for all aspects: all authors.

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Calidad seminal y ausencia RNA de SARS-CoV 2 en semen después de infección por COVID-19: un estudio observacional prospectivo y una validación de prueba de COVID en semen.

Objetivo: Estudiar la contagiosidad del semen y su influencia en la fertilidad después de la recuperación de infección por COVID-19.

Diseño: Estudio prospectivo de cohorte.

Escenario: Centro médico universitario.

Paciente(s): 120 hombres belgas recuperados de infección confirmada por COVID-19.

Intervención(es): no se realizó ninguna intervención.

Medida(s) de resultado principal: la calidad del semen fue abordada utilizando los criterios de la Organización Mundial de la Salud. El daño al ADN de las células espermáticas fue abordado cuantificando el índice de fragmentación de ADN y capacidad de tinción de alta densidad. Finalmente, anticuerpos anti spike-1 de SARS-CoV2, nucleares y receptores del dominio S-1 fueron medidos por Elisa e inmunoensayo de quimioluminiscencia respectivamente.

Resultado(s): RNA de SARSCov2 no se detectó en el semen durante el periodo de estudio en un plazo corto después de la infección ni después de periodos mayores. La motilidad progresiva media se redujo en un 60% de los hombres estudiados en un plazo corto tras infección por COVID-19 (1mes), 37% de los hombres estudiados de 1 a 2 meses después de la infección por COVID-19 y el 28% de los hombres estudiados después de dos meses tras infección por COVID-19. La cuenta media de espermatozoides se redujo en un 37% en los hombres estudiados en un plazo corto tras infección, 29% de los hombres estudiados de 1 a 2 meses post infección, y 6% de los hombres estudiados después de dos meses de la infección. La severidad de la infección y la presencia de fiebre no se correlacionó con las características del semen, pero hubo fuerte correlación entre las anormalidades del semen y los títulos séricos de anticuerpo anti-spike-1 y anti-dominio de unión a receptor de spike 1, pero no contra nucleótido. Niveles altos de anticuerpos anti-espermatozoides se desarrollaron en tres hombres (2.5%).

Conclusión(es): El semen no es infeccioso con SARS-CoV2 una semana o más post infección por COVID-19 (media 53 días). Sin embargo, las parejas que buscan gestación deben ser advertidas de que la calidad del semen después de infección por COVID-19 puede ser subóptima. El tiempo estimado de recuperación es de tres meses, pero se están realizando estudios de seguimiento para confirmarlo y determinar si ocurre un daño permanente en una minoría de los hombres.