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*Research Article*

# Impact of SARS-CoV-2 and Other Upper Respiratory Tract Viral Infections on Reproductive Parameters in Young Healthy Men with Mild Symptoms of Disease

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Data regarding excretion of SARS-CoV-2 in semen are inconclusive and counseling regarding risk of sexual transmission is still challenging. Our knowledge on the effect of upper respiratory tract infections (URTI) on male reproductive system is also scarce. Apart from negative effect of fever on spermatogenesis virtually no study has been able to compare reproductive parameters in men with COVID-19 or other URTI with predisease data. Eleven men who developed symptoms of URTI during the first and second wave of COVID-19 pandemic and who had preexistent fertility and hormonal data, participated in the study leaving sperm and blood samples. Three additional subjects were recruited among proven SARS-CoV-2 positive male hospital workers (without previous data). SARS-CoV-2 RNA was present in the ejaculate from 2 of 5 (40%) young men with mild COVID-19. In one of them viral particles could be detected in the semen sample 2 weeks after the first sampling. Men with any URTI showed higher LH ($p = 0.02$), lower sperm concentration ($p = 0.047$), and free testosterone ($p = 0.008$) when compared to their samples delivered 10 years earlier. When SARS-CoV-2 positive subjects were compared to subjects with other URTIs, no difference in levels of reproductive parameters or inflammatory markers was seen. In conclusion, SARS-CoV-2 RNA can be present in the ejaculate but does not seem to affect reproductive parameters any more than other viruses. However, mild URTI was shown to affect the sperm concentration, LH, and free testosterone negatively.

## 1. Introduction

The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 led to a global public health crisis shortly after its occurrence [1]. Although, thanks to vaccination programs, the COVID-19 pandemic seems being under control, SARS-CoV-2 is expected also in the future to be an important player in the panorama of respiratory tract infections [2]. The early stages of the pandemic provided unique opportunities to study the response to SARS-CoV-2 in the context of immunologically naïve subjects.

SARS-COV 2 is predominantly transmitted through respiratory droplets, but the virus has also been identified in tears, feces, and blood [3] raising the concerns of extra-respiratory transmission pathways. Other viruses with pandemic potential such as zika virus and ebolavirus have been described to be present in the ejaculate which, thus, possibly serves as a transmission pathway [4, 5].

Shortly after the initial outbreak of the pandemic, thousands of medically assisted reproductive treatments were suspended due to uncertainties regarding transmission risks. An initial report showed reassuring results as no viral particles were detected in semen samples [6]-findings later confirmed by a larger study [7]. However, other authors have reported existence of SARS-CoV-2 in seminal fluid [8] albeit failing to provide convincing evidence that the results were

not due to contamination, at the time of sample collection even after applying a more stringent protocol for semen collection [9]. Furthermore, several additional studies have failed to demonstrate presence of SARS-CoV-2 in semen.

The available data suggest that SARS-CoV-2 might affect the testicles and the male reproductive system. The ACE-2 receptor is suggested to take crucial part in the viral lifecycle [10]. Previous research has shown this receptor to be expressed abundantly in testicular tissue and polymorphism in the *ACE-2* gene have been associated with infertility [11]. If SARS-CoV-2 is expressed in the testicular tissue, it could not only be present in the seminal fluid but could also negatively affect testicular function after moderate infection.

Thus, the data regarding excretion of SARS-CoV-2 in semen are inconclusive and counseling regarding risk of sexual transmission still challenging. Furthermore, most of the available data comes from hospitalized patients, in most cases during the postviremic phase of the disease which might, at least in some cases, explain the negative finding when searching for SARS-CoV-2 in the ejaculate. The knowledge of the effect of respiratory tract infections on the male reproductive system, is still scarce. Apart from the negative effect of fever on spermatogenesis [12] there are virtually no studies exploring the effect of respiratory infections on male reproductive parameters. Regarding SARS-CoV-2, no study has been able to compare the reproductive parameters in COVID-19 patients with their predisease data.

Our main questions in this study were: Is SARS-CoV-2 present in seminal fluid during early stages of COVID-19 in unvaccinated men? Does COVID-19 affect semen parameters and hormonal status to a higher degree than other upper respiratory tract infections (URTI)? Is inflammation part of the pathogenetic mechanism linking URTI to impairment of the reproductive function? We also aimed to compare hormonal and sperm parameters during URTI : S with previously available clinical data.

## 2. Patients and Methods

*2.1. Study Population and Recruitment.* All participants in a cohort of 314 men, 18–19 years old, from the general population, gathered in 2010 [13] in order to study secular trends in male reproductive function were contacted by letter in summer 2020 regarding participation in this study. They were asked to contact us by telephone as soon as possible after developing symptoms of URTI. As symptoms were regarded either a combination or single presence of: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhoea.

Subjects were excluded if they were living in a distance from the hospital making them unable to provide a fresh semen sample at home and bring it to Skane University Hospital in Malmö, Sweden within an hour. Eleven men who had mild URTI responded and were included in the analysis. Two of them tested positive for SARS-CoV-2 by real-time PCR in nasopharyngeal (NPh) samples.

At later stage, in order to increase the number of SARS-CoV-2 subjects, three additional subjects were recruited among SARS-CoV-2 positive male hospital workers. For these three subjects no previous data regarding reproductive parameters exist.

*2.2. Study Design.* Subjects willing to participate received, by mail, a kit containing written information about the study, a written document of consent, and a wide-mouthed container for semen collection. Subjects with symptoms contacted the hospital by phone at onset of symptoms of URTI and were sampled within 48 hr after symptom onset at Skane University Hospital, between dates 2020-12-09 and 2021-05-01. NPh swabs and semen were collected for SARS-CoV-2 testing. Furthermore, a fasting blood sample, was taken before 10 AM. For one subject, no blood sample was taken.

If SARS-CoV-2 was detected the patients was repeatedly tested every 14 days until a negative NPh swab was obtained.

The data for the study were collected before vaccines against COVID-19 were approved by European Medicine Agency therefore none of the participants had been previously vaccinated against COVID-19.

*2.3. PCR Testing for SARS-CoV-2.* All semen samples and nasopharyngeal samples were analyzed for SARS-CoV-2 by real-time PCR at the Department of Clinical Microbiology, Lund, a diagnostic laboratory accredited to ISO-EN 15189 (Swedac). A slightly modified version of the PCR-assay published by Corman et al. [13] was used, and cycle threshold (CT) values were reported for the positive samples. Nasopharyngeal samples from 15 patients were primarily tested by FilmArray Respiratory Panel (BioFire (Diagnostics LLC, Utah, US). This assay does not report CT-values.

*2.4. Hormone Analysis and Conversion.* Testosterone, Luteinizing hormone (LH), Follicle stimulating hormone (FSH), Estradiol, and Sex Hormone Binding Globulin (SHBG) concentrations were analyzed in the serum samples according to standard protocol (supplementary document). Due to change in the methods of analysis for these hormones after 2010–2011, a conversion was performed according to Bobjer et al. [14] for comparison with the values obtained in 2010.

*2.5. Semen Analysis.* Semen was collected within 48 hr of symptom onset at home by subjects within 1 hr prior to the hospital visit. There was no period of abstinence specified. The men were instructed to wash hands before masturbation and avoid contamination with saliva or lubricants. Semen was ejaculated into a wide mouthed collection container and then kept close to the body for temperature regulation for the duration of journey to the hospital, which in each case lasted less than 1 hr. Semen analysis was performed according to the 2010 WHO guidelines [15].

*2.6. Sperm Chromatin Structure Assay.* Semen samples were stored at −80°C until Sperm Chromatin Structure Analysis (SCSA) was performed. The examination was done according to standard procedure at Reproductive Medicine, Skane University Hospital in Malmö by an experienced technician. Results were expressed as DNA fragmentation index (DFI)

Table 1: Men positive for SARS-CoV-2.

| Patient | Nasopharynx 1* | Ejaculate 1* | Nasopharynx 2* | Ejaculate 2* | Nasopharynx 3* | Ejaculate 3* |
|---|---|---|---|---|---|---|
| **1** | **Pos** | Neg | Neg | Neg | ND | ND |
| **2** | **Pos** | **Pos (26)** | Neg | **Pos (35)** | ND | DP |
| **11** | **Pos** | Neg | **Pos** | Neg | Neg | Neg |
| **12** | **Pos** | **Pos (28)** | **Pos** | Neg | Neg | Neg |
| **14** | **Pos** | Neg | **Pos** | Neg | Neg | Neg |

PCR results at the different visits. * = Visit ($x$) = CT value ND = not done (due to negative NPh PCR at Visit 2); pos = SARS-CoV-2 PCR; pos = SARS-CoV-2 PCR; neg. Positive cases are marked in bold text.

Table 2: Background characteristics.

| Subject | PCR SARS-CoV-2 in NPh | Age (yrs) | BMI (kg/m$^2$) | Smoking | Medical treatment |
|---|---|---|---|---|---|
| 1 | + | 29 | 25.7 | Previously | Sertralin |
| 2 | + | 29 | 25.8 | Previously | No |
| 3 | − | 28 | 20.6 | Yes | No |
| 4 | − | 29 | 24.4 | No | No |
| 5 | − | 29 | 21.7 | Previously | No |
| 6 | − | 28 | No data | *No data* | *No* |
| 7 | − | 30 | 22.5 | Previously | No |
| 8 | − | 29 | No data | Yes | No |
| 9 | − | 29 | 20.3 | Previously | Sertralin |
| 10 | − | 29 | 26.4 | No | No |
| 11 | + | 28 | 27.2 | Previously | Xyren, elvance, attentin |
| 12 | + | 29 | 27.5 | Yes | No data |
| 13 | − | 19 | 21.7 | No | No data |
| 14 | + | 50 | 23.8 | No | No data |

NPh, nasopharynx; BMI, body mass index.

and highly DNA stainable cell fragments (HDS). The full protocol has been described elsewhere [16].

*2.7. Inflammatory Markers.* Analysis of inflammation markers in semen were done with MSD Mesoscale sandwich method according to the manufacturer's instructions. For ejaculate, dilutions of 1 : 1 and 1 : 2 were used. Inflammation markers examined were VEGF, tumor necrosis factor beta (TNF-$\beta$), interferon gamma (IFN-$\gamma$), interleukin (IL) -10, IL-1$\beta$, IL-2, IL-4, IL-6, IL-8, and TNF-$\alpha$.

*2.8. Interview.* Subjects were interviewed by telephone with a questionnaire about factors possibly affecting their hormonal and/or fertility status including smoking habits and use of drugs. All results are self-reported except age and height which was retrieved from the existing data. Two subjects did not participate in the interview.

*2.9. Statistical Analysis.* Statistical analyses were done using IBM SPSS Statistics 27.0 (IBM, Chicago, IL, USA). Due to relatively few data points nonparametric testing was performed. Intra-individual changes were assessed using Wilcoxon Signed Rank test. Comparison between groups of SARS-CoV-2 positive and negative men were analyzed with Mann–Whitney-$U$ test. Subjects without preexisting data were excluded from comparisons of reproductive parameters obtained 10 years ago and present status. Group characteristics were presented as medians and range. Statistical significance was defined as $p$ values of $<0.05$

*2.10. Ethics.* This study was approved by Swedish Ethical Review Authority (Nr 2020-02465 and 2021-01122). All participants signed informed consent.

## 3. Results

*3.1. SARS-CoV-2 in Seminal Fluid.* At the first sampling, SARS-CoV-2 RNA was found in the ejaculate of 2 out of 5 subjects with positive NPh PCR tests (40%; 95% CI : 12%–77%). Viral RNA remained in the ejaculate of one of the men also at the second sampling, 14 days later, despite the virus not being detected in the NPh. Two patients were tested negative in the NPh at Day 14 and were therefore not followed further (Table 1). None of the subjects developed severe disease requiring further contact with the healthcare system. Background characteristics of the study subjects are presented in Table 2.

*3.2. COVID-19 Positive and Negative Subjects with URTI at Baseline Visit.* No statistically significant differences were observed between semen parameters, inflammatory markers in ejaculate as well as levels of reproductive hormones between the ones who tested positive for SARS-CoV-2 RNA and the ones in whom COVID-19 could not be detected (Tables 3 and 4).

Table 3: Reproductive parameters of SARS-CoV-2 positive men and men with other URTI (SARS-CoV-2 negative) at baseline visit.

| | Median (range) | | *p*-Value |
|---|---|---|---|
| | SARS-CoV-2 positive | URTI, but SARS-CoV-2 negative | |
| Sperm concentration ($10^6$/mL) | 36.0 (2.7–68.0) | 36.0 (2.4–182.0) | 0.89 |
| Morphology (% normal sperm) | 4.0 (1.0–6.0) | 5.0 (1.0–9.0) | *0.30* |
| Total motility, PR + NP (%) | 75.0 (53.0–78.0) | 75.0 (42.0–86.0) | 0.59 |
| Progressive motility, PR (%) | 57.0 (43.0–67.0) | 55.0 (30.0–86.0) | 0.59 |
| Ejaculate volume (mL) | 6.1 (2.4–18.3) | 3.9 (1.6–6.0) | *0.32* |
| DFI (%) | 18.0 (8.0–34.0) | 9.0 (3.0–22.0) | *0.10* |
| HDS (%) | 7.0 (2.0–11.0) | 9.0 (4.0–17.0) | *0.53* |
| FSH (IE/L) | 4.2 (3.2–4.9) | 5.5 (1.5–6.0) | *0.13* |
| LH (IE/L) | 6.0 (2.7–13.0) | 5.5 (2.8–11.0) | *0.84* |
| SHBG (nmol/L) | 33.0 (9.0–46.0) | 41.0 (15.0–56.0) | *0.16* |
| Testosterone (nmol/L) | 13.6 (6.0–15.0) | 15.0 (10.0–22.0) | *0.23* |
| Testosterone/SHBG | 0.4 (0.3–0.7) | 0.4 (0.2–0.85) | *0.95* |
| Free testosterone * (nmol/L) | 0.2 (0.187–0.387) | 0.270 (0.162–0.374) | *0.97* |

Mann–Whitney *U* test. *According to Vermeulen formula.

Table 4: Comparison of inflammatory markers in ejaculate between SARS-CoV-2 positive and negative patients with upper respiratory tract infection.

| | Median (range) | | *p*-Value |
|---|---|---|---|
| | SARS-CoV-2 positive | URTI, but SARS-CoV-2 negative | |
| IFN-$\gamma$ (pg/mL) | 1.3 (0.5–1.6) | 1.0 (0.4–1.9) | *0.44* |
| IL-10 (pg/mL) | 3.7 (0.4–49.8) | 1.0 (0.3–163.2) | *0.88* |
| IL-1$\beta$ (pg/mL) | 19.5 (2.5–31.2) | 3.9 (2.0–9.7) | *0.06* |
| IL-2 (pg/mL) | 15.9 (3.5–27.4) | 7.7 (3.1–159.2) | *0.64* |
| IL-4 (pg/mL) | 2.0 (0.4–3.4) | 1.4 (0.3–2.9) | *0.44* |
| IL-6(pg/mL) | 0.9 (0.4–0.9) | 0.5 (0.2–1.0) | *0.28* |
| IL-8 (pg/mL) | 927.7 (808.0–1788.5) | 852.8 (314.2–1,348.5) | *0.22* |
| TNF-$\alpha$ (pg/mL) | 115.1 (79.8–811.6) | 196 (25.5–1,301.2) | *0.64* |

Mann–Whitney *U* test.

Table 5: Reproductive parameters in four SARS-CoV-2 positive patients at Visit 1 (baseline) and 2 (14 days later).

| Pat: | Visit | PCR in ejaculate | FSH (IE/L) | LH (IE/L) | Testosteron (nmol/L) | Sperm conc. ($10^6$/mL) | DFI (%) | HDS (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | Neg | 3.7 | 7.6 | 15.3 | 59.0 | 19 | 9 |
| | 2 | Neg | 3.9 | 8.8 | 18.4 | 22.0 | 7 | 12 |
| 2 | 1 | **Pos** | 3.2 | 6.0 | 8.3 | 36.0 | 8 | 5 |
| | 2 | **Pos** | 4.0 | 6.1 | 12.6 | 55.0 | 4 | 5 |
| 12 | 1 | **Pos** | 4.2 | 3.6 | 6.2 | 24.0 | 17 | 11 |
| | 2 | Neg | 4.5 | 4.6 | 6.5 | 27.0 | 9 | 9 |
| 14 | 1 | Neg | 4.9 | 2.7 | 13.9 | 68.0 | 34 | 2 |
| | 2 | Neg | 5.5 | 2.8 | 14.5 | 180.0 | 51 | 1 |
| *p*-Value* | | | *0.07* | *0.07* | *0.07* | *0.47* | *0.72* | *1.00* |

Wilcoxon signed rank test. *Comparison between Visit 1 and visit 2. Positive cases are marked in bold text.

*3.3. Visit 1 vs. Visit 2 among COVID-19 Positive Subjects.* No statistically significant differences were observed between reproductive parameters at baseline visit and 14 days later. However, in all four men the FSH, LH, and testosterone levels were slightly higher at the time of second testing as compared to the initial test performed within 48 hr of symptom onset. In 3 of the 4 subjects sperm concentration was slightly higher in the second testing (Table 5).

*3.4. Time of Onset of URTI vs. 10 Years before.* Eleven of the tested subjects had available semen and hormonal data obtained 10 years earlier which were compared to the ones assessed at the URTI onset. When SARS-CoV-2 positive and negative cases were tested separately no statistically significant differences were observed. However, when all men who presented with URTI were pooled significant increase in LH ($p = 0.021$), decrease in free T ($p = 0.008$), and decline in

Table 6: Pooled analysis of reproductive parameters in men with URTI at time of symptom onset in comparison to the samples obtained 10 years ago.

| | Median (range) | | $p$-Value |
|---|---|---|---|
| | 2020–21 | 2010 | |
| Sperm concentration ($10^6$/mL) | 36.0 (2.7–21.0) | 107.0 (21.0–200.0) | **0.047** |
| Ejaculate volume (mL) | 4.3 (1.6–18.3) | 2.8 (0.7–5.7) | 0.11 |
| FSH | 3.5 (1.5–6.0) | 2.9 (1.6–6.7) | 0.08 |
| Testosterone | 15.0 (8.3–21.7) | 17.0 (12.0–24.0) | 0.07 |
| LH | 6.0 (2.8–13.0) | 4.9 (3.4–6.1) | **0.02** |
| SHBG | 41.0 (20–56) | 32.0 (18–57) | 0.11 |
| Free testosterone* (nmol/L) | 0.256 (0.162–0.374) | 0.365 (0.256–0.453) | **0.008** |

Wilcoxon signed rank test. *According to Vermeulen Formula. Positive cases are marked in bold text.

sperm concentration ($p = 0.047$) were seen. Borderline significance was noted even for FSH increase ($p = 0.08$) and testosterone decrease ($p = 0.07$, Table 6).

## 4. Discussion

In this study we found that at the early stage of mild COVID-19 infection SARS-CoV-2 RNA was present in ejaculate from 2 of 5 (40%) unvaccinated young men. In one of them viral RNA could be detected in the semen sample also 2 weeks after the first sample when interestingly the Nph swab was negative for SARS-CoV-2. Men with any URTI showed higher LH and lower sperm concentration when compared to their samples delivered 10 years earlier. Borderline significance was even noted for decline in levels of testosterone and FSH increase. When COVID-19 positive patients were compared to patients with COVID-19 URTI : S, we found no difference in levels of reproductive hormones, sperm parameters, and seminal nor inflammatory marker levels.

Detection of viral RNA in seminal fluid is potentially of great importance. Although CT values are difficult to interpret, [17, 18] presence of even of low-viral levels in ejaculate can have clinical significance due to yet unknown effects on the embryo, or due to the fact that semen, potentially, can serve as a way of transmission to the partner. Presence of SARS-CoV-2 RNA in urine is well documented [19] but only few studies have described existence of viral RNA in human semen. Li et al. [8] found presence of SARS-CoV-2 in semen, in six of 38 infected subjects. Most of the positive findings were in the acute phase of the disease, similarly to our study. Other authors have been able to detect few cases of SARS-CoV-2 RNA in semen [20] and in another study meticulous comparison of oropharyngeal and seminal bacterial flora could neither confirm nor rule out contamination by oropharyngeal secretions during semen collection [9].

However, in contrast to our findings other authors failed to find evidence of SARS-CoV-2 in semen [21–23].

Our result show that mild COVID-19 does not seem to affect the reproductive system to a higher degree than the other URTIs, nor does it induce a higher degree of inflammatory response during the first 14 days from the onset of symptoms. This is despite the fact that viral RNA was present in the ejaculate, which should indicate that some of the men have had viraemia.

Previous research has found higher levels of LH and prolactin [24, 25] and low testosterone [24, 26–28] among men infected with COVID-19. However, most of the studied subjects had severe COVID-19 disease of whom some required intensive care [29], making interpretation of causality and direction of associations difficult.

Holtmann et al. [30] found no negative effect on semen quality in patients with mild symptoms, similar to our findings, but in patients hospitalized with moderate symptoms reduced sperm quality was demonstrated. Other authors have reported significant decreases in semen quality [20, 31] associated with the severity of COVID-19 disease when compared to the healthy individuals [32]. However, none of the studies included comparison with data before the patients were tested for COVID-19 which makes conclusions regarding causal association between COVID-19 severity and impairment of the reproductive parameters difficult.

For the pooled group of men with URTI, comparison of reproductive data gathered 10 years earlier, a statistically significant decrease in total sperm count and an increase in LH was noted. Whether this can be an effect from having a mild viral infection per se, or simply due to normal aging and/or other lifestyle factors remains unclear. However, previous studies have shown this to be visible only after the age of 30 [33] whereas our group of men is still in their late 20's. To the best of our knowledge no research has addressed the question whether mild URTI has an impact on the reproductive parameters. Except what has been the case for COVID-19, the existence of concomitant respiratory illnesses is usually not taken into consideration when obtaining semen samples for insemination or IVF. Our data might indicate that even mild URTI may have a negative impact on sperm concentration and, thereby, outcome of a fertility treatment. This necessitates further studies in order to clarify the pathophysiological effect of various types of respiratory tract infections on male reproduction.

There are a number of limitations in our study. First, there was a low number of participants and a large number of tests, which increases the risk of both Type 1 and Type 2 statistical errors. Second, symptom severity was not taken into consideration. However, none of the participants was admitted to hospital care due to severe disease during the study period. We could not exclude contamination of the semen sample but we find it very unlikely because one of

the subject had a negative NPh swab test at the second sampling when SARS-CoV-2 RNA was detected in the ejaculate.

In the context of assessing effects of URTIs on male reproductive parameters, lack of 10-years follow-up samples from men not having URTI, limited the interpretation of the observed alterations in the levels of markers of a reproductive function.

One of the strengths in our study is inclusion of predominantly young males, without other concomitant diseases except for the mild course of respiratory tract infections. Preexisting data on reproductive parameters was available for 11 participants making it possible to compare reproductive data at SARS-CoV-2 symptom onset with their previous status. CT-values for the PCR tests allowed for semiquantitative estimation of viral load. The men included in the study were from the prevaccine stage of the pandemic and therefore with presumably naïve immune system to the infection.

## 5. Conclusion

In early stage of disease, SARS-CoV-2 RNA was present in the ejaculate of 40% of unvaccinated men with mild COVID-19 infection. Mild SARS-CoV-2 seemed not to have a greater impact on the reproductive system than other URTIs. However, we found an indication of decrease in free testosterone and sperm concentration as well as increase in LH and FSH levels linked to any mild URTI. The small group size is however a limiting factor and our results need to be confirmed in the larger studies of men with URTI.

## Data Availability

The (DATA TYPE) data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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