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Effect of SARS-CoV-2 on semen parameters: A meta-analysis of 39 articles from 15 countries

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 September 2023 and was last updated on 01 September 2023.

INTRODUCTION

Review question / Objective Continuous variables included sperm volume, concentration, vitality, motility, and immotility, total, motile, and progressively motile sperm count, progressive and non-progressive sperm motility, normal and abnormal sperm morphology, abnormal sperm head, neck, and tail, pH, and deoxyribonucleic acid (DNA) fragmentation index. The dichotomous variables included oligospermia, asthenospermia, teratospermia, and the presence of white blood cell (WBC).

Condition being studied Coronavirus disease (COVID-19), a pandemic that occurred since 2019, is the consequence of infection with a highly contagious coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 1, 2. The initial strain was first reported in Wuhan, China and soon aroused concern worldwide owing to its staggering deleteriousness and rapid transmission 1, 2. By October 2022, SARS-CoV-2 infection had taken more than 6 million lives worldwide, causing countless economic losses 3. Coronaviruses are enveloped viruses characterised by solar-corona-like surfaces attributed to spike (S) proteins arising from the virion surface 4. These viruses establish ecological diversity through frequent genetic recombinations and mutations 5. Coronaviruses operate according to their positive-sense single-stranded ribonucleic acid (RNA) genome 4. The genome of SARS-CoV-2 possesses 14 open reading frames responsible for the synthesis of 29 viral proteins 6, including 16 non-structural proteins for viral replication and transcription; the nucleocapsid, S protein, membrane protein, and envelope protein for the assembly and suppression of the immune response; and accessory proteins for the regulation of viral infection. Contact between the S

protein and angiotensin-converting enzyme 2 (ACE2) receptor instructs membrane fusion of the virus and host, following which the viral genome is released into the cell. Various transmission routes have been verified in COVID-19, including contact transmission, droplet transmission, aerosol transmission, and faecal-oral transmission 7, 8. Once the viruses infect the human body, they may incubate for 2.1–11.1 days 9, which are followed by a series of symptoms, including fever, cough, myalgia, fatigue, headache, haemoptysis, and diarrhoea 10, 11. Severe COVID-19 has deleterious effects on the lung parenchyma, leading to pneumonia or acute aspiratory distress syndrome 12. Therefore, treatment and prevention of COVID-19 are crucial for improving safety and quality of life and economic development.

Some viruses have displayed prejudicial effects on male reproductive function, including the mumps virus 13, the Zika virus 14, and the main virus investigated in this analysis, SARS-CoV-2. A study conducted during the early pandemic reported that 37% of the patients had decreased sexual activity and 44% had decreased sexual partners 15. This observation is considered to be the result of social isolation or COVID-19 consequent cardiovascular disease, leading to erectile dysfunction, and altered sexual desire and ejaculatory function 16. Additionally, the effects of COVID-19 on the male genital tract have been studied. Of all the surveyed individuals, 8 had scrotal discomfort, 14 had swelling, 16 had pain, and 1 had erythema. Moreover, according to the scrotal ultrasonography results, 10 patients had acute orchitis, 7 had acute epididymitis, and 16 had acute epididymal-orchitis 17. Regarding the effects of COVID-19 on semen parameters, some researchers have illustrated that patients with moderate COVID-19 show significant reductions in sperm concentration in semen, the number of sperms per ejaculate, and sperm motility, whereas the semen parameters of patients with mild COVID-19 do not significantly differ from those of controls 18. Although SARS-CoV-2 has been considered to harm the male genital tract and decrease semen parameters19, some relevant studies have shown that infection with SARS-CoV-2does not contribute to the decline in semen parameters. A multi-centre study by Paoli et al. showed that COVID-19 does not directly damage testicular function or semen parameters and its indirect damage seems to be temporary 20. Owing to the limitations of quality, sample size, and regional and racial differences in the original studies, the credibility of the results was limited, and different conclusions were drawn. Therefore, our study aimed to conduct a meta-analysis of original studies on the impact of SARS-CoV-2 on semen quality parameters to provide more reliable evidence for clinical practice.

METHODS

Participant or population Patients after SARS-CoV-2 infection.

Intervention Use of specific drugs.

Comparator Usual care or no care.

Study designs to be included We included articles published in English, with the study population divided into case and control groups.

Eligibility criteria We included articles published in English, with the study population divided into case and control groups. During the follow-up of patients after SARS-CoV-2 infection, semen parameters should be presented in the case group, regardless of age, sex, race, vaccination history, or differences in medication during treatment. Semen parameters for individuals not yet infected with SARS-CoV-2 should be presented in the control group. Single-arm studies or studies that only provided data on semen parameters at different follow-up time points after SARS-CoV-2 infection were excluded. Studies with incomplete data, such as continuous variables in which only the sample size, median, and interquartile range were provided were also excluded. For repeatedly published articles by the same author, those with a smaller sample size were excluded. Single-arm studies or studies that only provided data on semen parameters at different follow-up time points after SARS-CoV-2 infection were excluded. Studies with incomplete data, such as continuous variables in which only the sample size, median, and interquartile range were provided were also excluded. For repeatedly published articles by the same author, those with a smaller sample size were excluded.

Information sources PubMed, Embase, Web of Science, MedRxiv, BioRxiv, and World Health Organization Global Coronavirus databases were searched online for articles published between 1 January 2020 and 25 July 2023. Search terms included sperm, semen, seminal fluid, spermatozoa, fertility, infertility, COVID-19, Coronavirus Disease 2019, SARS-CoV-2, SARS Coronavirus 2, 2019-nCoV, and the 2019 Novel Coronavirus. Using PubMed as an example, Table 1 presents the search strategy.

Main outcome(s) In our meta-analysis examining the primary outcomes, two general parameters

(sperm volume and concentration), two sperm motility status parameters (sperm motility and immotility) and two sperm morphology parameters (normal and abnormal sperm morphology) were studied.

Quality assessment / Risk of bias analysis Quality of the articles was assessed using the Newcastle-Ottawa Scale, and original articles of poor quality were excluded from the meta-analysis.

Strategy of data synthesis The meta-analysis was performed using Review Manager 5.4 and StataMP 17. When the heterogeneity test showed P>0.05, the heterogeneity between studies was regarded as insignificant, and a meta-analysis was performed using a fixed-effects model. When the heterogeneity test showed P<0.05, heterogeneity between studies was regarded as significant; meta-analysis was performed using a random-effects model, and subgroup analysis was considered further. Continuous and dichotomous variables were characterised by the mean difference (MD) and odds ratio (OR), respectively. P0.05 indicating no significant publication bias.

Subgroup analysis For studies that provided subgroup data on severity and follow-up status, the data of each subgroup were recorded separately, in addition to the overall semen parameter data. If subgroup classification was based on other factors (e.g., body temperature, medication during treatment), only the overall data were extracted rather than the data of each subgroup.

Sensitivity analysis A sensitivity analysis was performed using a one-by-one exclusion method. For the sperm volume parameter of the overall meta-analysis, the MD values were all less than zero, and the P-values were all less than 0.05 after the exclusion of any single study, suggesting strong stability. For parameters such as sperm motility, the conclusion of greater stability can also be applied. However, for sperm concentration, total sperm count, sperm vitality, progressive sperm motility, DNA fragmentation index, and the presence of WBC, which were limited by factors such as heterogeneity and the number of included studies, a change in statistical significance after the exclusion of a single original study was observed. These results suggest that for these six parameters, the conclusions are vulnerable to changes in a single study, whereas the meta-analysis conclusions for the other parameters have strong stability.

Country(ies) involved China.

Keywords SARS-CoV-2; COVID-19; semen; sperm; meta-analysis.

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