Semen parameters in men recovered from COVID-19: a systematic review and meta-analysis

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Systematic Review

Keywords: Semen, Sex hormones, COVID-19, SARS-CoV-2, Meta-analysis

Posted Date: September 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-912054/v1

Version of Record: A version of this preprint was published at Middle East Fertility Society Journal on December 1st, 2021. See the published version at https://doi.org/10.1186/s43043-021-00089-w.

Abstract

Background: The novel beta-coronavirus disease (COVID-19) has infected millions of people globally with high risk among male then female. However, the effect of COVID-19 andrology is still a subject of dispute. We planned to analyze the overall consequences of COVID-19 on semen parameters and male sex hormones.

Main text: Systematic search was performed on MEDLINE and Scopus database until June 11 2021. We included observational studies, which reported mean ± standard deviation of the semen parameters and serum sex hormones of those reproductive-aged male recovered from COVID-19 and controls who did not suffered from COVID-19. We used Random-effect model to pool the studies, as heterogeneity was present. Heterogeneity was evaluated by Q test and I^2. All studies were assessed with their quality and publication bias.

We assessed 966 articles for eligibility and found 7 eligible studies meeting PICO criteria. This include 934 participants with mean age 37.34 ± 10.5. Random-effect model meta-analysis showed that men recovered form COVID-19 had semen parameters less than those who had not suffered from COVID-19. The overall mean difference (MD) [95% confidence interval (CI)] in semen volume, sperm concentration, sperm number, and progressive sperm motility was -0.20 (-0.45, 0.05), -16.59 (-34.82, 1.65), -45.44 (-84.56, -6.31), -1.73(-8.20, 4.75) respectively. Considering sex hormones; Luteinizing hormone and prolactin was found more among those recovered with the significant MD (95% CI) of 3.47 (1.59, 5.35) and 3.21 (1.71, 4.72) respectively.

Conclusion: Both the semen parameters and sexual hormones were found to be affected after infected with COVID-19. However, the mechanism for testicular involvement remains doubtful.

This systematic review and meta-analysis has been registered in PROSPERO (ID: CRD42021259445)

Background

The novel beta-coronavirus also called severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has infected millions globally since first reported from Wuhan, China, on 31 December 2019[1]. Its common symptoms include dry cough, fever, malaise, dyspnea, and fatigue. Due to its rapid spread and multiple organ damage, concerned authorities and healthcare workers have taken significant measures to address this pandemic[2 3].

Studies have shown the disease to affect different systems of the body. Recently, SARS-CoV-2 RNA has been found in the semen of a COVID-19 patient - however, this has been a disputed issue. Li et al.[4] conducted a study on male patients with COVID-19 and those recovering from the disease, identified SARS-CoV-2 in semen. In contrast, other studies on acutely infected and recovered patients of COVID-19 did not report SARS-CoV-2 RNAs in the semen[5 6]. Studies have shown the utilization of angiotensin-

converting enzyme II (ACE2) as a receptor by SARS-CoV2 to enter the host cell[7]. An expression profile of a single-cell-human RNA found that Leydig, Sertoli, and spermatogonial cells are enriched with ACE2[8].

A study from Yang et al. revealed COVID-19 patients with an impairment in testicular histology, morphological changes in Sertoli cells, decreased Leydig cells, and lymphocytic inflammation[9]. These changes reflect the unfavorable effect of COVID-19 on the male reproductive system. A longitudinal study carried out among those recovered from COVID-19 observed a negative impact on sperm quality, although these were likely to be reversible[10]. However, Holtman et al. found out that adverse effects on sperm count and sperm motility were only detected in hospitalized patients but not in subjects who have recovered after mild symptoms[11]. Overall, there are varying results regarding the sexual hormone secretion among those recovered from SARS-CoV2[10 12 13].

Recent evidence is inconclusive regarding the effect of COVID-19 on the male reproductive system. Exploring the overall impact of COVID-19 on the semen parameter and male reproductive hormones may also contribute to further investigation into male reproductive endocrinology. To our knowledge, a meta-analysis on semen analysis among patients recovered from COVID-19 lacks to date. Therefore, we aim to investigate the overall difference in semen parameters and male sex hormones between those recovered from COVID-19 and those not infected.

Methodology

We registered this study in the PROSPERO (CRD42021259445) before conducting the research. We followed the PRISMA guidelines to perform and report this systematic review and meta-analysis[14]. We performed a comprehensive literature searching of PubMed/Medline, Scopus databases by two independent reviewers since inception until 11 June 2021 to find the relevant papers. We also explored the references in the retrieved articles. The used search string composed of following key-terms: “COVID 19,” “corona virus,” “coronavirus,” severe acute respiratory syndrome coronavirus 2,” “SARS CoV2,” “semen,” “sperm,” and “seminal.” The two reviewers screened all the studies by title, abstract and keywords. If in need of more information’s, full-text was referred. Two independent reviewer extracted the data from the study selected and stored in the spreadsheet electronically. The information included first author’s name, date of publication, design, location, sample size, characteristics of study participants including mean age, mean BMI (Body mass index), duration of the symptom. For semen analysis, we evaluated; collected semen volume milliliter (mL), total sperm number (millions per ejaculate), sperm concentration (millions/mL), progressive motility (%), sperm vitality (%), and sperm morphology (%). We also evaluated the sex hormones levels: follicle-stimulating hormones (FSH), luteinizing hormone (LH), progesterone, testosterone, prolactin, and inhibin where possible. Total participants (N), mean and standard deviation (SD) of all these mentioned parameters were extracted for those recovered from COVID-19 and healthy/non- COVID groups. Studies were included if: they analyzed the semen and/or sex hormones among the recovered male patients to find the impact of COVID-19 on male reproduction. Semen samples were obtained by masturbation and then ejaculation into sterile containers[10 11 15]. Sperm

was analyzed according to the WHO laboratory manuals[16]. For hormonal analysis, the peripheral blood sample was used[12 13 17]. Studies were excluded if published in a language that could not be translatable, multiple publications, or those with incomplete data after 2 attempts to contact the authors.

Two independent reviewers (ST and RS) assessed the risk of bias for each study using the Newcastle Ottawa scale (NOS) adapted for cross-sectional, case-control, and cohort studies[18]. This scale rated the quality of the study in three main domains for each study design: selection, comparability, and outcome. The maximum score was nine. Disagreements were solved by a discussion between two reviewers (SB, AG), which was later reviewed by the principal investigator (NK).

For pooling effect sizes, direct meta-analysis was performed, including unstandardized mean difference (MD) of semen parameters and sex hormones in subjects recovered from COVID-19 and non-COVID recovered patients. Q test and I^2 statistics were applied to assess heterogeneity between studies[19]. The presence of heterogeneity was claimed if a p-value of the Q test was >0.1 or I^2 statistic was less than 25%. Mean differences (MD) were pooled across studies using the inverse variance method if they were homogeneous; otherwise, DerSimonian and Laird method was used. Publication bias was assessed by a funnel plot and Egger's test[20]. A p-value of < 0.05 was considered statistically significant except for heterogeneity it was < 0.1. We performed all the analyses using STATA software, version 16.1 by StataCorp (College Station, Texas).

Results

We identified 206 and 760 studies from MEDLINE via PubMed and Scopus, respectively (Fig. 1). Of them, 7 studies met our eligibility criteria. Characteristics of the 7 studies are described in Table 1. There were 5[12 13 21 22], 1[10], and 1[11]cross-sectional, case-control, and cohort studies, respectively. The participants either recovered from COVID-19 or were without a history of COVID-19 infection – and had a mean age and BMI of 37.34 ± 10.5 and 25.6 ± 0.65, respectively. These studies were conducted in China[10 13 17 21], Turkey[22], and Germany[11]. The risk of bias assessment of the studies are presented in the Supplemental Tables 1. All the included studies were of good quality.

Considering the semen analysis, the followings component were analyzed:

Semen volume

According to the meta-analysis from 5 studies [10–12 21 22], subjects recovered from COVID-19 have semen volume about 0.2ml less than those without COVID-19 (Overall MD: -0.20; 95% CI: -0.45, 0.05) (Fig. 2). However MDs between-study were moderately varied (p = 0.20, I^2 = 33.79%). The funnel plot was symmetrical, corresponding to Egger's test (coefficient = -1.3, standard error (SE) = 0.93, p = 0.17) (Supplemental Figure).

Sperm concentration

Subject recovered form COVID-19 have sperm concentration about 16.59 *10^6 ml less than those without COVID-19 (Overall MD -16.59, 95% CI: -34.82, 1.65) (Fig. 2). This MDs between 4 studies[10 11 21 22] were highly varied ($p < 0.01$, $I^2 = 92.06\%$). The funnel plot was asymmetrical, corresponding to the Egger's test (coefficient = -2.19, SE = 0.959, p = 0.022). A contour-enhanced funnel plot showed the missing study in the non-significant area indicating asymmetry might be due to publication bias. However, meta-trim suggested no missing studies concluding that the asymmetry was not due to missing study rather heterogeneity might be the cause (Supplemental Figure).

Total Sperm number

MD from 5 studies[10–12 21 22] were highly varied ($p = 0.02$, $I^2 = 71.47\%$). There was statistically significant pooled MD (95% CI) of -45.44 (-84.56, -6.31) suggesting that those recovered form COVID-19 have sperm number less than 45.4*10^6 per ejaculation (Fig. 2). The funnel plot was symmetrical corresponding the Egger test (coefficient = 0.95, SE = 0.91, p = 0.29) (Supplemental Figure).

Progressive sperm motility

According to the meta-analysis from 5 studies[10–12 21 22], progressive sperm motility of those subjects recovered from COVID-19 was 1.73% less than those without COVID-19 (Overall MD: -1.73; 95% CI: -8.20, 4.75; p = 0.20, $I^2 = 89.49\%$) (Fig. 2). The funnel plot was symmetrical, corresponding to Egger's test (coefficient = 1.77, SE = 0.93, p = 0.06) (Supplemental Figure).

Sperm motility

MD from 5 studies [10–12 21 22] were highly varied ($p \leq 0.001$, $I^2 = 75.35\%$). There was statistically significant pooled MD (95% CI) of -10.02 (-15.30, -4.74) (Fig. 2) suggesting that those recovered form COVID-19 have total sperm motility less than about 10%. The funnel plot was symmetrical corresponding the Egger test (coefficient = -1, SE = 0.81, p = 0.21) (Supplemental Figure).

Vitality

MD from 2 studies[10 22] were highly varied ($p = 0.23$, $I^2 = 82.98\%$). The pooled MD was − 3.51(-7.86, 0.84) (Fig. 2).

With respect to the male sex hormones,

FSH:

According to the meta-analysis from 4 studies[10 12 13 17], FSH among those subjects recovered from COVID-19 was 0.09 (mIU/mL) less than those without COVID-19 (Overall MD: -0.09; 95% CI: -0.32, 0.15; p = 0.26 $I^2 = 26\%$) (Fig. 3). The funnel plot was symmetrical, corresponding to Egger's test (coefficient = -1.34, SE = 0.75, p = 0.07) (Supplemental Figure).

LH

Meta-analysis from 4 studies[10 12 13 17] revealed that subject recovered from COVID-19 was 3.47(mIU/mL) more than those without COVID-19 (overall MD: 0.15; 95% CI -2.013, 2.316). However, MD between studies were highly varied (p = < 0.001, I^2 = 99.07%) (Fig. 3). The funnel plot was asymmetrical corresponding to the Egger's test (coefficient = -2.78, SE = 1.74, P = 0.11). A contour-enhanced funnel plot showed the missing study in the non-significant area indicating asymmetry might be due to publication bias. Therefore, the meta-trim fills method was used which suggests no missing studies (Supplemental Figure). Thus, we conclude that the asymmetry was not due to missing study but heterogeneity might be the cause for asymmetry.

Testosterone

Testosterone among those recovered from COVID-19 is less than that in non-COVID overall MD: -0.051 95% CI (-0.277, 0.175) (Fig. 3). MD between these 4 studies[10 12 13 17] were moderately varied (p = 0.10, I^2 = 51.96%). The funnel plot was symmetrical corresponding to the Eggers test (coefficient = -0.28, SE = 1.03, p = 0.73) (Supplemental Figure).

Prolactin

Prolactin level among those recovered from COVID-19 was more than that among non-COVID-19 groups with overall MD (95% CI) of 3.21 (1.71, 4.72) with the presence of low heterogeneity (p = 0.21, I^2 = 34.39%) from 3 studies[10 12 17] (Fig. 3). This signifies the level of Prolactin was about 3(ng/ml) times more among those recovered from COVID-19.

Estradiol

Estradiol level among those recovered from COVID-19 was more than those non-COVID-19 groups and this MD between 3 studies were moderately varied: overall MD (95% CI) of 4.87 (0.88, 8.85; I^2 = 68.87%, p = 0.04) (Fig. 3).

Discussion

Looking into the effect of COVID-19 on semen and fertility of males recovered from COVID-19, we compared the overall semen analysis and sex hormone profile between the recovered COVID-19 patients and those without COVID-19 infection. Lesser semen volume, sperm concentration, and progressive sperm motility were found among those recovered from COVID-19 although not significant. Similarly, statistically significant MD of sperm number and total sperm mortality between the COVID-19 group and those without COVID-19 infection was observed. Regarding the hormones, statistically significant higher LH and Prolactin were found among those COVID-19 patients. However, the overall FSH and testosterone were more among those non-COVID-19 patients although non-significant.

The male reproductive function might be affected by a wide range of viruses including influenza, mumps virus, Zika virus, Human immunodeficiency virus (HIV), and even may infect testes [23]. Other than the direct effects of the virus on the testes, there are several other indirect factors such as inflammation,

fever, and the dysregulation of the hypothalamic–pituitary–gonadal axis, which may cause the impairment of testosterone secretion or sperm production.

The long-term and duration of effect on male fertility by SARS-CoV-2 is still subject of debatable. The SARS-CoV and SARS-CoV-2 showed almost similarities in the full genomic sequences, they both have ACE2 receptor and spike protein (protein S) to enter the host cell. The protein S is filled by a transmembrane serine protease (TMPRSS2). Sertoli cells, Leydig cells, prostatic epithelial cells, and Spermatogonia all express TMPRSS2 and ACE-2 receptors [8]. Overall, the way of transmission and genetic similarity of the SARS-COV-2 virus affects men than females (male: female ratio 2.7:1) than SARS-CoV, hence its effect on male reproductive function is a subject of research [24]. Although the most common manifestation of COVID-19 is pneumonia due to the occupancy of ACE2 containing cells, ACE2 receptors are also present in most organs. As the study revealed that the Sertoli and Leydig cells have a higher level of ACE2 receptor than type II alveolar cells, this makes the testicles at risk to SARS-CoV-2. Although there is expression of ACE2 receptor in the testicular tissue, no clear evident regarding the testicular infection due to COVID-19 is a big issue. The virus reaches the lungs by the inhalation of droplets but there are no any direct way to reach the testes and other targeted organs which can be the logic for the respiratory symptoms being more characteristics.

As SARS-CoV-2 was detected in the semen in recent studies, it could be sexually transmitted[10 11]. Although Machado et al, detected a viral RNA in one case out of 15 study participants, the methodology used was not mentioned. They mentioned that masturbation as one of the collection methods for semen samples could cause contamination through hand and even cough. The observed decrease in the semen parameters could be due to the injury from the SARS-COV-2 infection by the immune response in opposition to the seminiferous epithelium[24]. Like most infectious diseases, a decrease in testosterone level can be due to the inflammatory process enhanced by fever, which damages the germ cells by infiltration. It could be even due to a breach on the barrier of blood-testis[25]. The increased level of LH could be due to the compensated hypogonadism[26]. Some of the studies reported that some cytokines as the putative markers of infections[27]. Interleukins-8 is involved in the inflammation of seminal vesicles, prostate ad epididymis which makes it a marker for male accessory gland infection[28 29]. Furthermore, the different procedures during treatment like; ventilation support, use of sedative drugs, steroids, antibiotics, organ support therapy, and so on and even the distress can affect the function of testis[30]. But most of our study participants were tested after they were tested COVID-19 negative, the impact of inflammatory process by fever on the semen quality seems to be minor. Also, we should keep in mind that the variety of psychological and environmental factor play a role. The stressful events from COVID-19 ultimately make the sex less desirable. Hence, those recovering should also focus on their psychological state and considering the counseling may benefit to some extent.

However, there are some limitations of this meta-analysis. Most of the included studies were cross-sectional design, so causal association between COVID-19 and the semen parameters along with sex hormones could not be worked out. Heterogeneity was high between included studies. Other clinical

characteristics that may have caused heterogeneity but the data were not available for subgroup analysis.

In conclusion, the semen parameters were found to be affected by the SARA-CoV-2. This raises the possibility that SARS-CoV-2 could affect the sexual development and fertility of males. However, more future prospective cohort studies will need to prove and simplify the association.

Declarations

Competing interests: The authors declare no competing interests.

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Table 1

Author (year)	Country	Design	Mean age	Mean BMI	Outcomes	
					Semen analysis	Sex hormones
Erbay (2021)[22]	Turkey	Cross-sectional	30.68	25.28	Semen volume, sperm concentration , Total sperm number, Progressive sperm motility, vitality	
Guo (2021)[10]	China	Case-control	27.55		Semen volume, Sperm concentration, Total sperm number, Progressive sperm motility, Sperm motility, Vitality	Estradiol, FSH, LH, Testosterone, Prolactin, Inhibin
Holtman (2021)[11]	Germany	Cohort	38.2	25.2	Semen volume, Sperm concentration, Total sperm number, Progressive sperm motility, Sperm motility	Estradiol
Ma (2021)[13]	China	Cross-sectional	38.2			FSH, LH, Testosterone
Raun (2021)[21]	China	Cross-sectional	30.8		Semen volume, Sperm concentration, Total sperm number, Progressive sperm motility, Sperm motility	
Temiz (2021)[12]	Turkey	Cross-sectional	36.6	26.6	Total sperm number, Progressive sperm motility, Sperm motility	FSH, LH, Testosterone, Prolactin
Xu (2021)[17]	China	Cross-sectional	59.2	25.5		Estradiol, FSH, LH, Testosterone

Units of semen analysis according to WHO fifth edition, Semen volume (ml), Sperm concentration ($\times 10^6 ml^{-1}$), Total sperm count (millions per ejaculate), Progressive sperm motility (%), Sperm motility (%), Sperm vitality (%), WBC (x 10^9/L). Unit of sex hormones, Estradiol (pg ml^{-1}), FSH (U l^{-1}), LH (U l^{-1}), Testosterone (ng ml^{-1}), Prolactin (ng ml^{-1}). FSH: follicle stimulating hormone; LH: luteinizing hormone;

Figures

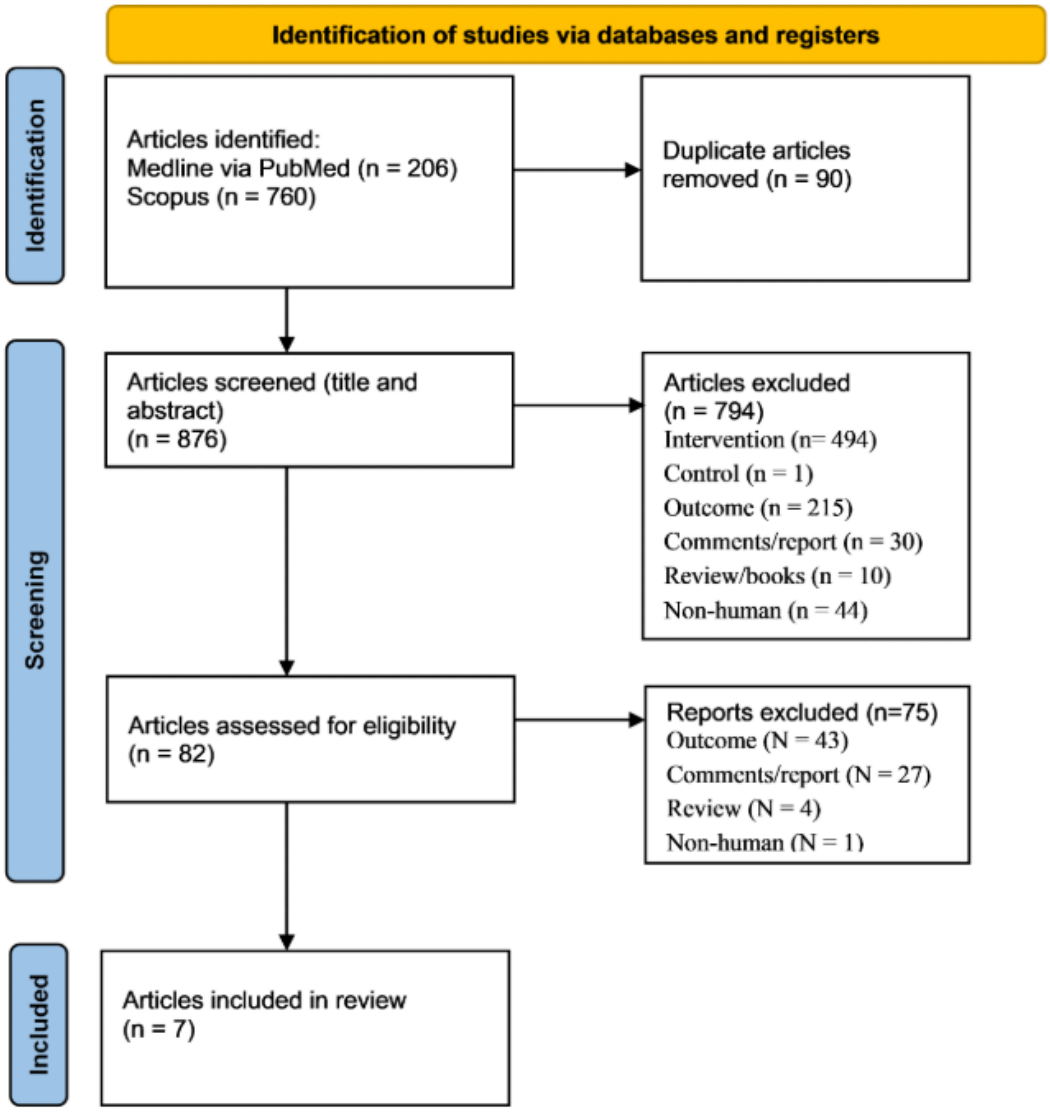

Figure 1

PRISMA flow diagram

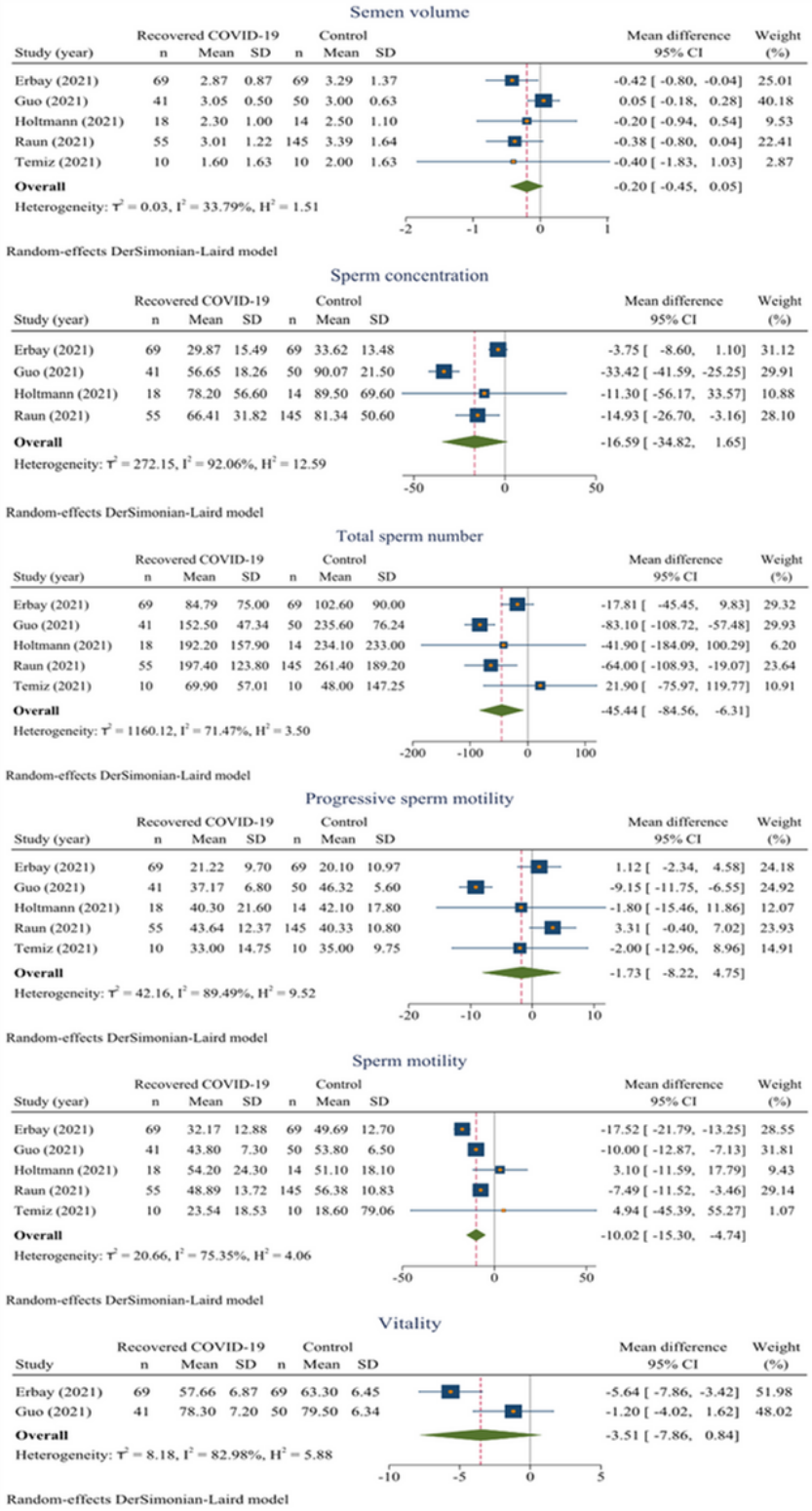

Figure 2

Forest plots for estimation of pooled mean difference of semen analysis

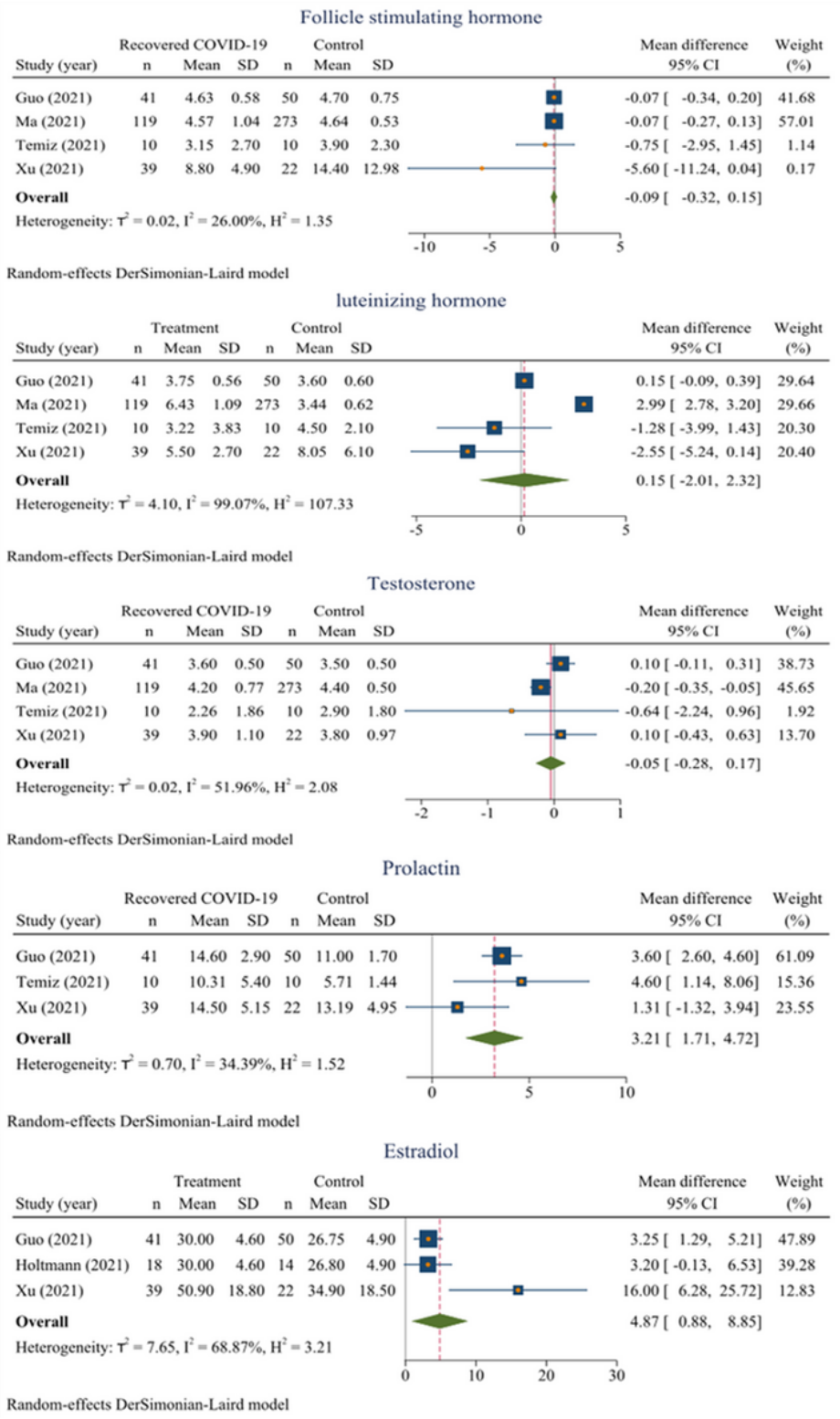

Figure 3

Forest plots for estimation of pooled mean difference of male sex hormones

Supplementary Files

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