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Impact of COVID-19 vaccination on seminal and systemic inflammation in men

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ABSTRACT

Expedited development of SARS-CoV-2 vaccines led to public concerns regarding impacts of the novel vaccine on gametes in patients seeking assisted reproduction. In cases of an acute intermittent illness or fever in men, it is often advised to postpone ART treatments so that efforts can be made to enhance wellbeing and improve sperm parameters. However, it is unknown whether sperm parameters are altered in the acute (24–72 hour) phase following COVID-19 vaccination. We performed a longitudinal cohort study of 17 normospermic male patients attending a fertility clinic for semen analysis. Semen and matched peripheral blood samples were collected prior to vaccination, within 46 $\pm$ 18.9 hours of vaccine course completion (acute) and at 88.4 $\pm$ 12 days (3 months) post-vaccination. No overall change from baseline was seen in symptoms, mean volume, pH, sperm concentration, motility, morphology or DNA damage in the acute or long phase. Seminal plasma was found to be negative for anti-SARS-CoV2 Spike antibody detection, and MCP-1 levels showed an acute but transient elevation post-vaccine, while IL-8 was marginally increased 3 months after completion of vaccination. A modest, positive correlation was noted between serum levels of the anti-inflammatory cytokine IL-10 and self-reported symptoms post-vaccine. Our findings are reassuring in that no significant adverse effect of vaccination was noted and provide evidence to support the current recommendations of reproductive medicine organisations regarding timing of vaccination during fertility treatment.

1. Introduction

SARS-CoV-2 or COVID-19 infection is now recognised as a multi-system disease. While its effects on the male reproductive system are not yet fully understood, potential mechanisms described include direct viral invasion into testicular tissue (Yang et al., 2020, Ma et al., 2021), endocrinological interference with reproductive function (Rastrelli et al., 2020, Salciccia et al., 2020), and inflammatory-mediated reproductive dysfunction (Holtmann et al., 2020, Takahashi et al., 2020, Tian and Zhou, 2021). The extent of SARS-CoV-2 involvement in male reproduction is conflicting (He et al., 2021), though several studies have demonstrated a deterioration in sperm parameters both during and after SARS-CoV-2 infection (Mannur et al., 2021). Falahieh et al. studied 20 men in both the acute and recovery phase (Falahieh et al., 2021). Sperm parameters, including motility and DNA fragmentation, showed improvement at 120 days relative to 14 days post-infection. Interestingly, reactive oxygen species (ROS) and malondialdehyde, a marker of oxidative stress, were significantly reduced at 120 days, with a

Abbreviations: ART, assisted reproductive technology; IVF, in vitro fertilization; DFI, DNA fragmentation index.

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concomitant increase in total semen antioxidant capacity. Several studies have failed to demonstrate SARS-CoV-2 RNA in the semen of either acutely infected men or those in the recovery phase (Holtmann et al., 2020, Pan et al., 2020, Song et al., 2020, Guo et al., 2021). Yang et al. examined testicular tissue from 12 deceased SARS-CoV-2 patients and although interference with testicular parenchyma was identified, only one sample was confirmed to contain the virus (Yang et al., 2020).

The rapid emergence of COVID-19 vaccines created an air of uncertainty and vaccine hesitancy among men of reproductive age in many jurisdictions (Turocy et al., 2021, Mascherini and Nivakoski, 2022). A study of IVF outcomes in 36 couples who had treatment cycles pre-vaccination and in the 7–85 days post a second dose of mRNA SARS-CoV-2 vaccine showed no significant difference in sperm motility, concentration or volume, or in ovarian response, fertilisation and blastomere formation (Orvieto et al., 2021). A further study in 45 men prior to and 75 days post-mRNA vaccine showed no significant decrease in sperm parameters (Gonzalez et al., 2021). Liftshitz et al. looked at semen parameters 1–2 months following the second dose of a mRNA SARS-CoV-2 vaccine, and found no significant effect when compared to the normal reference range set out by the WHO (Lifshitz et al., 2022). Additional work looking specifically at the BNT162b2 vaccine also found no significant difference between pre- and post-vaccine semen parameters in male fertility patients (Ferraro et al., 2022), while seminal plasma reactive oxygen species, cell membrane activity markers and IL-6 levels were similarly unchanged at 3 months post-vaccination (Olana et al., 2022). A recent systematic review and meta-analysis of the impact of COVID-19 infection and vaccination on male fertility highlighted the marked variability of sperm parameters and outcome measures between studies, but supported the prevailing view that mRNA vaccines do not have long-term detrimental effects on male reproductive function (Edele Santos et al., 2023).

At least one international body initially declared that "*it seems prudent to postpone the start of assisted reproduction treatments for at least a few days after the completion of vaccination to allow time for the immune response to settle*" (European Society for Human Reproduction ESHRE, 2021). Indeed, previous studies have shown an acute impact of pyrexia or febrile illness on sperm parameters (Carlsen et al., 2003, Sergerie et al., 2007), both during the meiotic and post-meiotic period of spermatogenesis (Carlsen et al., 2003). Given that few studies to date have looked at sperm parameters in the very acute phase following COVID-19 vaccination, and that aggressive host inflammation and cytokine responses are a well-documented hallmark of SARS-CoV2 infection, the aim of this study was to determine whether sperm parameters and circulating (serum) and local (seminal fluid) COVID-19 antibodies, inflammatory cytokines and chemokines are altered within the 24–72 hour period post-vaccination. The goal is to provide evidence to support the recommendations of international bodies regarding the appropriate timing of vaccination in relation to ART treatment and to add objective scientific information to the debates around vaccine hesitancy.

2. Methods

2.1. Study design

For this longitudinal cohort study, participants were asked to provide a blood and semen sample at three separate timepoints: prior to first vaccine dose (T=0), at <72hrs following completion of the vaccine program i.e., after receiving the second dose of Pfizer/BioNTech COVID-19 (BNT162b2) or first dose of Jcovden (Janssen) recombinant Ad26-COV2 DNA vaccine (T=1) and at 3 months (70–90 days) after vaccine completion/second vaccine dose (T=2). Demographic details and post-vaccination symptoms were documented. Systemic symptoms (headache, fatigue, chills, diarrhoea, fever, myalgia, and vomiting) as well as local side-effects at the injection site (local pain, swelling, redness) were self-reported on a scale of 1 (none) to 4 (severe). Using an anticipated effect size (Cohen's d) of 1.42, based on serum cytokine level changes in the acute phase (24hrs) post influenza vaccination reported in a previous study (Talaat et al., 2018), the recruitment target was 24 patients to detect a significant difference between baseline and acute post-vaccine cytokine levels with 90 % power and type I error rate of 0.05.

2.2. Patient selection

Eighty-five men of reproductive age (≥18 yrs to ≤50 yrs) with a scheduled appointment for routine semen analysis at the clinic over an 8-week period (June 2021 to July 2021, inclusive) were invited to participate. Those with a chronic underlying health condition, taking regular medication, prior vaccination or a history of confirmed SARS-CoV-2 infection were excluded. To facilitate identification of a clinically significant drop in sperm parameters following vaccination, men with an abnormal baseline semen analysis were excluded following the preliminary result and informed of this on the day of the initial sample receipt. A clinically relevant change in sperm parameters (count, motility) was defined as one that re-classified the semen analysis result from 'normal' to subnormal as per WHO thresholds (World Health, 2021). Normal morphology is widely considered a more subjective marker of sperm quality, and a poor predictor of pregnancy potential, therefore deviations in this parameter at baseline did not result in exclusion from the study (Danis and Samplaski, 2019). Changes in morphology post vaccine were, however, included. Six men had an initial low morphology result (<4 %) but all had a normal level at some stage during the study, confirming the variability of this marker.

2.3. Sample collection and semen analysis

Study participants provided a semen sample following 2–7 days of abstinence, as per WHO guidelines (World Health, 2021). Sperm concentration, motility and morphology, as well as seminal fluid pH, was measured. For sperm DNA fragmentation analysis, 0.5mls of semen was mixed 1:1 with TNE-buffer (SDI®-test, SPZ Labs, Denmark). Per SPZ labs classification, DNA fragmentation index (DFI) value of <15 % denotes low DNA fragility and a 'normal' result, 15–25 % indicates 'reduced fertility', while >25 % indicates 'strongly reduced fertility'. Blood samples for serum isolation were taken via peripheral venepuncture.

2.4. Enzyme-linked immunosorbent assay (ELISA)

Quantitation of inflammatory mediators in serum and seminal plasma was performed using commercially available ELISA kits (BioLegend ELISA Max), following the manufacturer's protocols. Immune factors assayed were: IL-6, IL-8, IL-10, IFN-γ, TNF-α, IFN-γ-induced protein 10 (IP-10; CXCL10), and monocyte chemoattractant protein 1 (MCP-1; CCL2). Frozen samples were thawed and processed to fit the detection range of each kit: serum samples were analysed undiluted, seminal plasma samples were analysed as follows: undiluted (TNF-α, IFN- γ, IL-6, IL-10); two-fold dilution (IL-8) and ten-fold dilution (IP-10, MCP-1). Absorbance values were measured on SPECTRAmax PLUS 384 Microplate Spectrophotometer (Molecular Devices).

2.5. Serological ELISA for detection of human anti-SARS-CoV-2 spike isotypes IgA, IgM and IgG1

Samples were screened using an anti-SARS CoV-2 spike ELISA assay for three relevant antibody isotypes: IgG1, IgM and IgA (23). Paired sera and seminal plasma samples were diluted 1:50 with 1 % non-fat milk in PBS-0.1 % Tween 20 (PBST) and 100 μL added to wells. ELISA protocol was based on a published method (Amanat et al., 2020), as described in detail by Phelan et al. (Phelan et al., 2021). Optical density was measured at 492 nm using a Multiskan FC (Thermo Fisher Scientific, Waltham, MA, USA) plate reader.

2.6. Statistical analysis

Data was analysed using GraphPad Prism version 9.3 (GraphPad Software, La Jolla, CA). Descriptive statistics presented are median, interquartile range (IQR), mean and standard deviation (SD). Spearman's rank correlation was used for correlation analyses. Comparisons between pre- and post-vaccine outputs used repeated measures one-way ANOVA or Friedman test with Dunnett's or Dunn's post-test for multiple comparisons, respectively. Categorical variables were analysed using χ^2 test or a Fisher's exact test where appropriate; p-value of <0.05 was considered significant.

2.7. Ethical approval

The study, conducted at a private, not-for-profit fertility clinic associated with a tertiary university maternity hospital, was approved by the National Maternity Hospital Research Ethics Committee (reference EC33.2020). Written consent was obtained from all participants.

3. Results

3.1. Patient recruitment and demographics

Of sixty-four male patients eligible for study inclusion, thirty-six men declined at outset to participate (Fig. 1). Reasons included vaccine hesitancy (27.8 %, n=10), geographical distance from the clinic (22.2 %, n=8) or time constraints (13.9 %, n=5). Paired serum and seminal plasma samples were acquired for 17 subjects, ranging in age from 27 to 40 years, with mean BMI of 25.9 $\pm$ 3.5 kg/m^2 (Table 1). Acute (T=1) samples were acquired within 46 $\pm$ 18.9 hours of vaccine course completion and final (T=2) samples were acquired within 88.4 $\pm$ 12 days. Median self-reported symptom score post vaccine regimen completion was 3, ranging from 1 to 10 (Table 1).

Table 1
Demographics of study participants (n=17).

Characteristic	Value (n=17)
Age, years (mean $\pm$ SD)	34.7 $\pm$ 3.8
BMI, kg/m^2 (mean $\pm$ SD)	25.9 $\pm$ 3.5
Smoker, n (%)	
No	14 (82)
Yes	3 (18)
Previous paternities*, n (%)	
None	10 (59)
1	5 (29)
>1	2 (12)
Total symptom score	3.6 $\pm$ 2.7
T=1: Hours post vaccine**	46 $\pm$ 18.9
T=2: Days post vaccine***	88.4 + 12

*includes miscarriage
**time interval (hours) between vaccine completion and collection of semen and blood sample (post t=1)
***days between vaccine completion and collection of semen and blood sample (post t=2)

3.2. Sperm parameters pre- and post-COVID vaccination

As shown in Table 2, there was no overall change from baseline in mean volume, pH, sperm concentration, motility, morphology or DNA

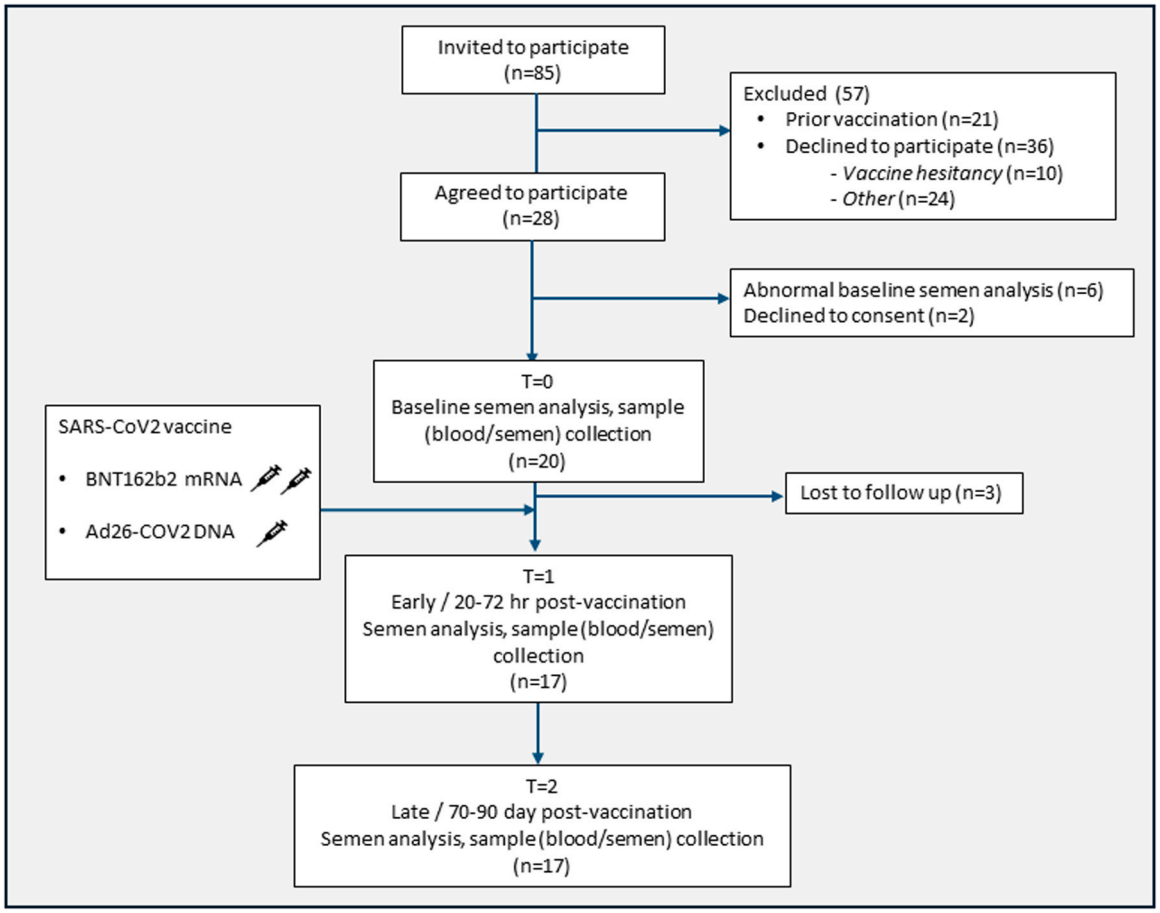

Fig. 1. : Cohort recruitment and sample collection. Schematic representation of patient selection, inclusion and timeline of matched semen and peripheral blood sample collection before and after vaccination. BNT162b2: Pfizer/BioNTech COVID-19; Ad26-COV2 DNA: Jcovden (Janssen) recombinant DNA vaccine.

Table 2
Sperm parameters before and after SARS-Co-V2 vaccination.

Parameter	Normal (WHO, 2021)	Median (IQR)			P-value
		Pre-vaccine (t=0)	Post-vaccine (t=1)	Post-vaccine (t=2)	
Semen volume (ml)	>1.5	3.7 (2.3–4.9)	3.9 (3.3–5.1)	3.8 (3.1–5.7)	0.133
Sperm concentration (million/ml)	>15	54 (27–72.3)	60 (42.8–75.3)	64 (35.5–89)	0.251
Motility (%)	>42	57 (47.5–64.5)	57 (46–67.5)	56 (45.5–60)	0.280
Normal morphology (%)	>4	4 (2.5–4.5)	5 (3–5)	4 (2.5–5.5)	0.668
pH		7.8 (7.6–8.0)	7.8 (7.6–8.0)	7.8 (7.6–7.9)	0.346
DNA fragmentation index; DFI (%)		8.98 (5.2–11)	8.53 (4.2–12.2)	9.2 (4.5–12)	0.943

IQR: interquartile range
Statistical significance determined by repeated measures one-way ANOVA (parametric; sperm concentration) or Friedman test (non-parametric) with Dunnett's or Dunn's post-test for multiple comparisons, respectively.

fragmentation in the acute phase or longer-term phase post-vaccine completion. Individual results are shown in Supplementary Figures 1 to 5; all parameters showed wide inter-individual variability, clinically significant changes were noted in two men in the acute phase (T=1). Patient 12 showed a marked decrease in sperm motility from 40 % to 6 %, with an increase in sperm DNA fragmentation index (DFI) from 9.9 % to 16.1 %, but a low self-reported symptom score. Motility increased to 28 % and DFI was reduced to 11.2 % by 3-months. Patient 15 also showed a large decrease in sperm motility (45–7 %) at (T=1), with a corresponding increase in DFI (from 25 % to 50.4 %). By three months, motility and DFI had returned to 50 % and 19.6 % respectively.

3.3. Detection of circulating and local SARS-CoV-2 anti-spike antibody isotypes

As displayed in Fig. 2, none of the pre-vaccine serum samples showed immunoreactivity with IgG1 anti-Spike antibody, with twelve and fifteen samples showing IgG1 seropositivity at the acute and long term timepoints, respectively. One patient showed pre-vaccine immunoreactivity to IgM (Patient 17) and one to IgA antibody (Patient 15), suggesting a potential recent subclinical infection in each of these two patients. As outlined above, Patient 15 displayed an acute reduced sperm motility post-vaccine, with a return to normal at 3 months. Four out of 17 (23.5 %) samples were negative for all three isotypes (IgM, IgA, IgG1) at acute phase completion, while one (Patient 5) remained negative for all antibodies at 3 months. Previous work has indicated that antibody responses to the BNT162b2 mRNA vaccine are inversely correlated with age (Arunachalam et al., 2021). However, in our patient cohort, no correlation was observed between subject age at vaccination and Ig seropositivity at T1 (Spearman r= - 0.099, p=0.701) or at T2 (Spearman r= −0.11, p=0.677).

Seminal plasma samples were also screened for Ig isotypes. To rule out the possibility that factors present in seminal plasma could interfere with Ig detection, a commercial positive anti-Spike control was used to confirm detection in the ELISA assay (data not shown). As outlined in Fig. 2, all seminal plasma samples were found to be negative for anti-SARS-CoV2 antibodies.

3.4. Analysis of Inflammatory mediators in serum and seminal plasma pre and post vaccine

Chemokine MCP-1 (CCL2) was detected in both serum and seminal plasma, with 10-fold higher levels measured in semen as compared to serum (Fig. 3). IL-10 was detectable in serum alone (Fig. 3A). Interindividual variation for all inflammatory proteins was found to be high, even at baseline. In the acute phase, MCP-1 was found to be modestly increased in seminal plasma (2358 ± 1008 pg/ml vs 1824 ± 1105 pg/ml) and decreased in circulating serum (160.8 ± 81.95 pg/ml vs 202.7 ± 40.24 pg/ml) relative to pre-vaccine levels (Figs. 2B and 2C). While seminal MCP-1 levels had normalized by 3-months (2025 ± 1131 pg/ml), serum MCP-1 was further decreased relative to pre-vaccine levels (120.3 ± 65.39 pg/ml). A small but significant increase was also noted in seminal plasma IL-8 levels at 3-months compared to pre-vaccine baseline levels (619.4 ± 686.8 pg/ml vs 320.2 ± 336.2 pg/ml).

To determine if there was any association between clinical factors (BMI, post-vaccine symptom score) and inflammatory mediator levels in the acute post-vaccine phase, Spearman correlation analysis was performed. As shown (Fig. 4), symptom score positively correlates with serum IL-10 (r=0.64, p=0.0067), with modest correlation between seminal plasma MCP-1 and IL-8 levels (r=0.5, p=0.044), as well as between serum MCP-1 and IL-10 (r=0.51, p=0.037). No correlation was found between BMI and any of the inflammatory proteins profiled. We further investigated whether sperm parameters correlated with inflammatory mediators in the acute post-vaccine phase. While a modest

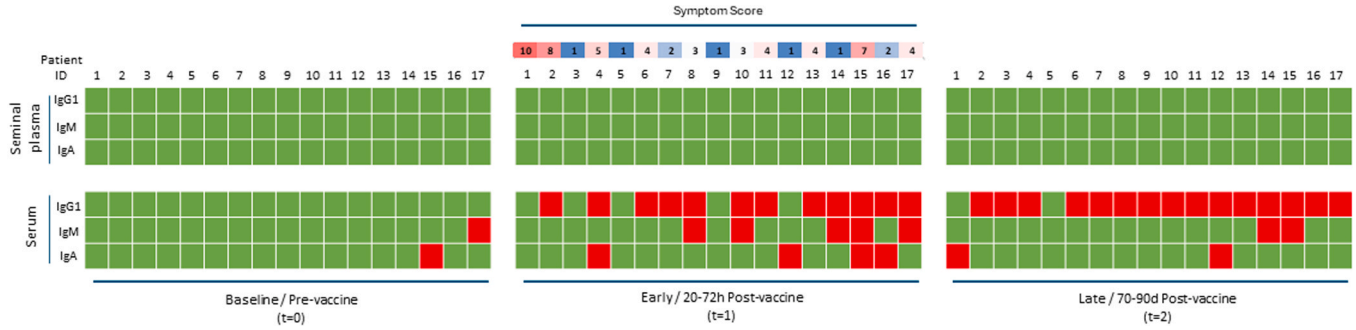

Fig. 2. : Anti-SARS-Co-V2 (anti-spike) IgG1, IgM and IgA immunoreactivity in patient semen and blood samples pre and post vaccination. Seminal plasma and serum samples were screened for anti-SARS-Co-V2 Ig isotypes by ELISA at three timepoints: t=0: baseline (pre-vaccination); t=1: 'early' post-vaccination phase i.e. within 72 hours of vaccine regimen completion (Patient 1: after one dose of recombinant Ad26-COV2 DNA vaccine; Patients 2–17: after second dose of BNT162b2 mRNA vaccine); t=2: 'late' post-vaccination i.e. 70–90 days after vaccination. Symptom score in early post-vaccination phase was calculated for each patient from self-reported systemic symptoms (headache, fatigue, chills, diarrhoea, fever, myalgia, and vomiting) as well as local side-effects at the injection site (local pain, swelling, redness). Green: negative for Ig; red: positive for Ig.

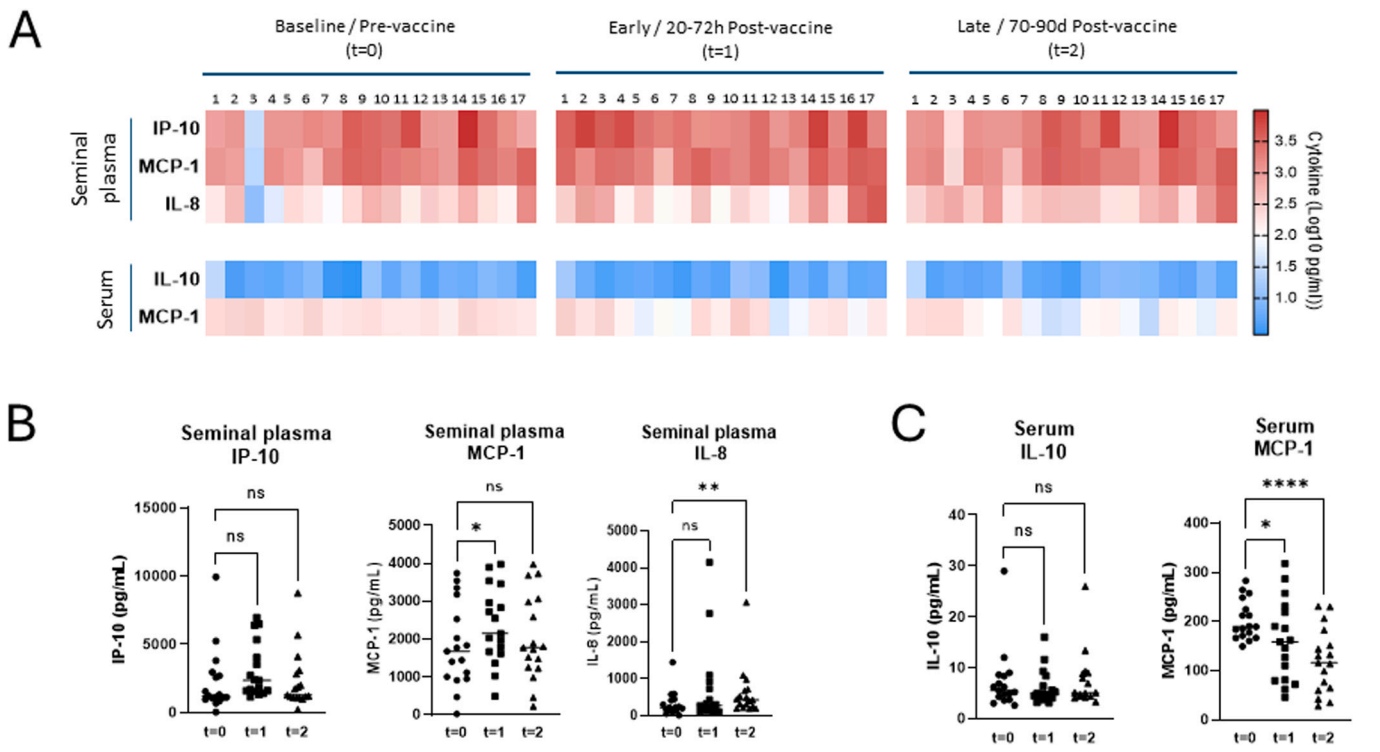

Fig. 3. : Seminal plasma and serum cytokine profiles before and after the SARS-CoV2 vaccine. (A) Heatmap of log10 transformed cytokine concentrations in seminal plasma and serum samples collected from study participants (n=17) pre-vaccination (t=0), after vaccine completion (t=1) and 70–90 days post vaccination (t=2). (B, C) Cytokine/chemokine levels (pg/ml) in seminal plasma samples and serum samples, respectively; each data point corresponds to an individual subject at each timepoint. IP-10: Interferon gamma-induced protein 10 (CXCL10); MCP-1: Monocyte chemoattractant protein-1 (CCL2); IL-8: interleukin 8; IL-10: interleukin 10. *p<0.05; **p<0.01; ***p<0.0001, Friedman test for non-parametric data, with Dunn's post-test for multiple comparisons.

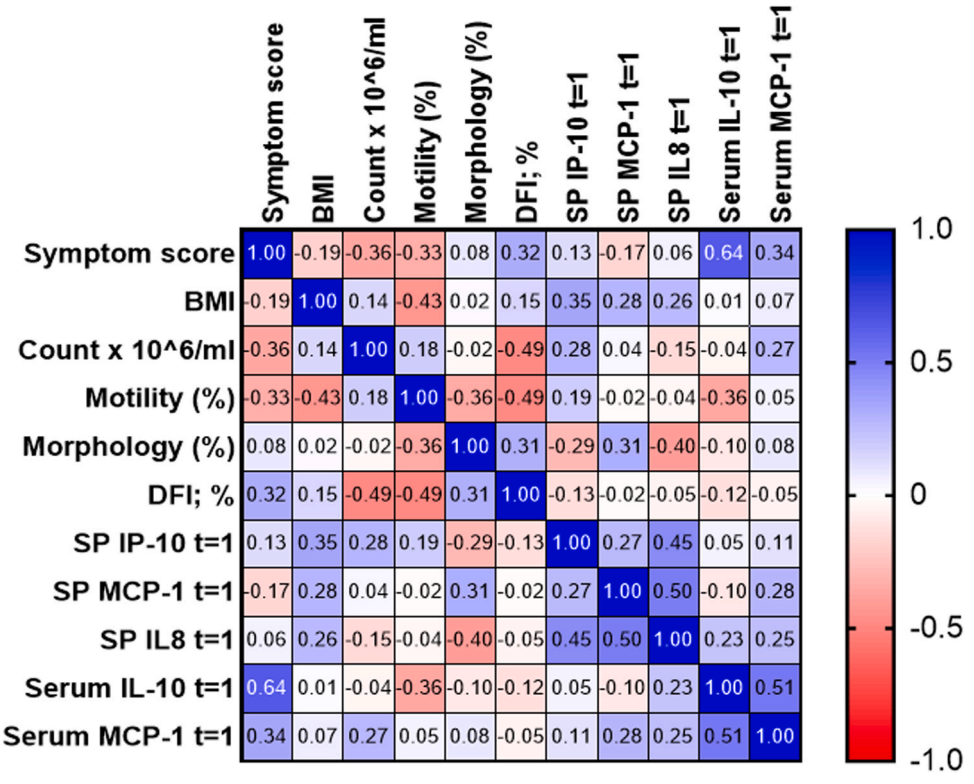

Fig. 4. : Association of clinical factors and sperm parameters with inflammatory mediators. Correlation matrix showing Spearman r values. BMI: body mass index; symptom score: self-reported symptoms after vaccine regimen completion; DFI: sperm DNA fragmentation index; IP-10: Interferon gamma-induced protein 10 (CXCL10); MCP-1: Monocyte chemoattractant protein-1 (CCL2); IL-8: interleukin 8; IL-10: interleukin 10.

negative corelation was found between DFI and sperm count (r= −0.49, p=0.05), as well as sperm motility (r= −0.49, p=0.05), there was no association between cytokine levels and any sperm parameters tested (Fig. 4).

4. Discussion

International guidance in ART initially recommended avoiding vaccination in the days prior to and directly following treatment, to avoid potential misinterpretation of vaccine-related symptoms as a complication of treatment, such as infection after oocyte retrieval (Bfs, 2021). Subsequently, updated ESHRE and BFS guidance advised "*men and women attempting to conceive through assisted reproduction receive the COVID-19 vaccine before starting treatment or at any time during fertility treatment*" (27) and that those undergoing fertility treatment should "*have the vaccine when offered it*" (Bfs, 2022).

Concerns regarding the influence of acute inflammation on semen analyses were also noted by the Societies for Male Reproduction and Urology (SMRU) and for the Study of Male Reproduction (SSMR). Acute systemic inflammatory responses have been observed with other viral vaccines (Eriksson et al., 2007, Talaat et al., 2018). In a study of inactivated trivalent influenza vaccine, Taalat et al. reported elevations in serum IFN-γ and IP-10 (CXCL10) one day after vaccination, and a similar response was observed with the monovalent 2009 H1N1 vaccine (Sobolev et al., 2016). In contrast, systemic levels of the pro-inflammatory cytokine IL-8 were reduced after influenza vaccination, remaining reduced for up to 14 days (Talaat et al., 2018).

MCP-1/CCL2 and IP-10 are key chemokines for antigen presenting cell activation and migration while IL-8 is a known granulocyte chemotactic factor and phagocytic stimulant (Deshmane et al., 2009, Costela-Ruiz et al., 2020a). Semen from healthy fertile men contains many immunologic factors, with modest to high levels of IL-8 and MCP-1 being universally present (Politch et al., 2007). Increased seminal MCP-1 has also previously been described in male patients hospitalized with SARS-Co-V2 infection (Bendayan and Boitrelle, 2020), while another study revealed pathological levels of seminal IL-8 (i.e. >3800 pg/ml) in 76 % of previously infected men (Gacci et al., 2021). Our findings also indicate a modest, positive correlation between serum levels of the anti-inflammatory cytokine IL-10 and self-reported symptoms post-vaccine. Increased IL-10 has been linked in several studies to COVID-19 disease severity and progression (Costela-Ruiz et al., 2020b), suggesting IL-10 may show promise as a prognostic marker (Wang et al., 2020).

A large U.K. study of vaccinated adults found that 96.42 % (95 % CI 96–96.79) developed antibodies 28–34 days after the first dose, increasing to 99.08 % (95 % CI 97.8–99.62) within 7–14 days of the second dose. In our study, 16 subjects received two doses of Pfizer BioNTech vaccine, with 14–28 days between first and second dose; of these, 13 (81.25 %) were seropositive for anti-SARS-Co-V2 antibodies in samples collected within 20–72 hours of the second vaccine dose. Sensitivity of the serological IgA assay used in our study has been estimated at 43 % and may be attributable, in part, to the primary association of IgA with immune responses at mucosal surfaces (Phelan et al., 2021). Published studies of COVID-19 antibody isotype kinetics show a similar profile to other acute viral infections; IgM has been shown to peak at 15–35 days post symptom onset and then decline, in contrast to IgG, which plateaus around 22–35 days post symptom onset (Kweon et al., 2020).

In their study of ovarian follicular fluid from women post-COVID-19 infection or vaccination, Bentov et al. (Bentov et al., 2021) detected similar levels of anti-SARS-Co-V2 IgG antibodies in follicular fluid as those found in serum. Our findings, using a validated ELISA-based assay, strongly indicate that SARS-Co-V2 antibody isotypes are negligible in seminal fluid of vaccinated men. One recent study contradicts this (Chillon et al., 2023). However, several anomalies are noted. First, while the authors describe a strong correlation between serum and seminal SARS-Co-V2 antibody titres, the majority of seminal plasma samples from vaccinated subjects show no increased neutralizing activity compared with unvaccinated samples. Indeed, while the prior COVID infection status of subjects is not disclosed, background neutralizing activity in unvaccinated seminal samples ranges as high as 40 %. Second, increasing seminal antibody titres did not show strong correlative increases in neutralizing activity (R=0.38), unlike in serum (R=0.54). These discrepancies raise questions regarding the functionality of described seminal plasma anti-SARS-Co-V2 antibodies and highlight the need for further studies.

Limitations to our study include the small cohort size of 17 patients, despite initial invitations to 85 men. Due to the efficient national roll out of the COVID-19 vaccination programme in Ireland, recruitment of non-vaccinated men proved particularly challenging. Additionally, while the WHO recommends performing semen analysis at least twice due to known high interindividual variability in sperm parameters, it was not feasible for study subjects to provide more than one sample for each timepoint. It would be prudent to consider other potential impacts of the vaccine on fertilisation, embryo development and pregnancy rates in this subgroup of patients if treatment proceeds in the acute phase following vaccination. These outcomes were not addressed in our study and require further analysis.

5. Conclusion

In cases of an acute intermittent inflammatory illness, it is often advised to postpone ART treatments so that efforts can be made to enhance wellbeing and improve sperm parameters. Our findings in the acute immune response phase following vaccination support international recommendations on timing of vaccination relative to treatment.

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CRediT authorship contribution statement

Laurentina Schaler: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Jordi Guardiola:** Data curation, Formal analysis, Investigation. **Magda Ghanim:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Louise Glover:** Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Mary Wingfield:** Conceptualization, Formal analysis, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Vincent Kelly:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft. **Gareth Brady:** Formal analysis, Methodology, Resources, Writing – original draft, Funding acquisition. **Aya Ibrahim:** Formal analysis, Methodology. **Niall Conlon:** Conceptualization, Funding acquisition, Methodology, Resources. **William McCormack:** Formal analysis, Funding acquisition, Methodology.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jri.2024.104287.

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