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Short Communication

Potential Relationship between Recent COVID-19, Autoantibody Profile, and Outcomes of Assisted Reproductive Technology Cycles in Non-Vaccinated Women

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ABSTRACT

The observational prospective study included 240 non-vaccinated against COVID-19 women aged 18-40 years without systemic autoimmune diseases who applied for infertility treatment using ART. Patients were divided into two groups: group 1-105 patients without a history of COVID-19; group 2-135 patients who had mild (n=85) or moderate COVID-19 (n=50) less than 12 months prior to Transvaginal Oocyte Retrieval (TOR). The profile of serum autoantibodies, parameters of oogenesis, embryogenesis, and clinical ART outcomes were assessed. Potential relationship between recent COVID-19 (<180 days before TOR), its severity, detected autoantibodies, and poor reproductive outcomes including early miscarriage, has been found.

Keywords: COVID-19; SARS-CoV-2; Autoantibody profile; Assisted reproductive technology; Reproductive outcome

DESCRIPTION

The new RNA Betacoronavirus, namely Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), was the cause the first cases of Corona Virus Disease in 2019 (COVID-19) in humans, and in March 2020 World Health Organization (WHO) announced a COVID-19 pandemic. SARS-CoV-2 infection can trigger such immunopathological mechanisms as inflammation, apoptosis, endothelial dysfunction, cytokine storm, complement and coagulation hyperactivation [1]. Remarkably, the expression of Angiotensin-Converting Enzyme 2 (ACE2), the main cellular SARS-CoV-2 receptor, and co-receptor transmembrane serine protease 2 was found not only in epithelial cells of respiratory tract, but also in cells of the endometrium, placenta, ovaries, fallopian tubes, and embryo [2]. Moreover, ACE2 is an important component of the renin-angiotensin system, dysregulation of the latter can lead to impaired folliculogenesis, ovulation, and corpus luteum function [3].

In addition, SARS-CoV-2 has similarities with other viruses that trigger autoimmunity: induce production of autoantibodies, cause a strong type I interferon response, trigger autoimmune disorders in susceptible people [4]. Moreover, viral proteins, in particular the S protein, contain superantigenic motifs and peptide sequences homologous to fragments of human proteins. In severe COVID-19, B-lymphocytes and plasma cells can develop from naive B cells along the extrafollicular pathway [5]. All of the above predisposes to triggering an autoimmune process that can affect fertility or Assisted Reproductive Technology (ART) outcomes.

We investigated the effect of COVID-19 of varying severity and associated autoantibodies on reproductive outcomes in ART cycles with fresh oocytes retrieved at different time intervals after the disease [6].

The observational prospective study included 240 women aged 18-40 years without systemic autoimmune diseases who applied

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for infertility treatment using ART from September 2020 to December 2021. Patients were divided into two groups: group 1-105 patients without a history of COVID-19; group 2-135 patients who survived mild (subgroup 2a, n=85) or moderate COVID-19 (subgroup 2b, n=50) less than 12 months prior to Transvaginal Oocyte Retrieval (TOR).

To confirm the diagnosis of COVID-19 and detect re-infection, nasopharyngeal swabs were screened using real-time reverse transcription polymerase chain reaction, and serum antibodies to SARS-CoV-2 were determined using Enzyme-Linked Immunosorbent Assay (ELISA). The profile of serum autoantibodies, including Antiphospholipid (aPL), antinuclear and anti-thyroid antibodies, was studied prior to the ART cycle.

In all ART cycles, a protocol of controlled ovarian stimulation with a gonadotropin-releasing hormone antagonist was used [6]. The frequency of intracytoplasmic sperm injection for egg fertilization in two groups did not differ (86.7% *vs.* 91.8%; p=0.192), in other cases, *in vitro* fertilization was used.

Group 2 differed from group 1 by a higher body mass index in patients and a higher incidence of ear, throat, nose diseases and allergic disorders, 93.3% of them had Immunoglobulin G (IgG) antibodies against SARS-CoV-2. No differences were found between the parameters of oogenesis, embryogenesis, pregnancy and live birth rates in patients of these groups, as well as in patients with mild or moderate COVID-19. However, when TOR was performed less than 180 days after COVID-19, a higher proportion of poor quality blastocysts was obtained (p=0.006). Moreover, the risk of early miscarriage in patients with moderate COVID-19 was 4.2 times higher than in patients without a history of COVID-19 (p=0.036).

Although the rate of detection of total aPL in two groups did not differ (29.5%; 31.3%; p=0.79), in group 2, antibodies to Phosphatidylethanolamine (PE) and Annexin V (An V) were revealed more often than "criteria" aPL (to cardiolipin, β2-glycoprotein-I). IgG antibodies to PE and An V were detected in group 2 (8.1%; 6.7%) and in subgroup 2b (8%; 10%) more often compared with group 1 (0.95%; 1.9%; $p<0.05$). The median level of anti-PE IgG was higher in group 2 than in group 1. Moreover, IgG antibodies to the Thyroid Stimulating Hormone Receptor (TSHR) were revealed more often in post-COVID-19 patients (8.2% *vs.* 1.9%, p=0.033). A negative correlation was found between the level of anti-PE IgG and the number of obtained mature oocytes (r=-0.129, p=0.045) and zygotes (r=-0.132, p=0.041). Importantly, antibodies to PE and An V were found in 3 out of 6 patients with early miscarriage.

CONCLUSION

In non-vaccinated patients who have had mild and moderate COVID-19 less than 12 months before TOR, parameters of oogenesis and embryogenesis, rate of pregnancy in ART cycles did not differ from those in patients without a history of COVID-19. However, patients who had survived COVID-19 less than 180 days prior to TOR had a higher proportion of poor quality blastocysts, and patients with moderate COVID-19 had an increased rate of early miscarriage. In post-COVID-19 patients, there was a higher frequency of detection of antibodies to PE and An V, as well as antibodies to TSHR, and an inverse correlation between the level of anti-PE IgG and the number of obtained oocytes and zygotes. All of the above suggests a possible adverse effect of COVID-19 and associated autoantibodies on the outcomes of ART cycles and early pregnancy. Clinical and laboratory monitoring, including autoantibody screening, in post-COVID-19 patients will allow to identify autoimmune disorders that may affect reproductive outcomes.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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