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Research Article

SARS-CoV-2 infection does not affect ovarian reserve in women undergoing assisted reproduction

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Summary

Information regarding the effects of the novel coronavirus on human reproduction is currently limited. The objective of our work was to assess whether, in women who have passed the disease, there was a variation in the ovarian reserve through the determination of AMH levels. During May-June 2020, women performing an Assisted Reproductive treatment and who had a positive IgG for SARS-CoV-2 were included in the study; this group of women had a previous AMH determination of no more than 6 months. Women were stratified into two groups, according to their previous AMH levels: low responders (AMH<1 ng/ml) or normal-high responders (AMH ≥ 1 ng/ml) Statistical analyses were performed using the Statistical Package for Social Sciences 19.0 (IBM Corporation, Armonk, NY, USA). A total of 46 patients were included in the study; 16 women were diagnosed as having low ovarian reserve (AMH < 1 ng/ml), with an average age of 38.6 years, whereas 30 were classified as having normal ovarian reserve (AMH ≥ 1 ng/ml), with an average age of 34.7 years. Generally, the data show no variation in AMH levels before and after SARS-CoV-2 infection (1.73 ng/ml *vs.* 1.61 ng/ml, respectively). However, when we analyzed these differences according to the study groups, the results were consistent with the patient's ovarian status. It is possible to conclude that the fact of having passed the disease does not affect the ovarian reserve status but the degree of the variation of AMH levels depending on the patient was a low or high responder.

More Information

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Introduction

Despite the overwhelming magnitude of the pandemic and its worldwide prevalence, information regarding the effects of the novel coronavirus on human reproduction is still limited [1]. As the assisted reproductive technology programs resumed operations, it was important to gather information regarding the status of individuals infected with the novel coronavirus and to assess gametes and reproductive outcomes for those who had the SARS-CoV-2 virus.

SARS-CoV-2 infection has been reported to have multi-system complications in addition to respiratory symptoms [2]. One possible mechanism might be that the virus might enter host cells through its receptor, angiotensin-converting enzyme-2 (ACE2); therefore, organs with high expression of ACE2 might be attacked by this virus. In a previous animal study, ACE2 expression has also been reported in ovarian granulosa cells [3] which means the ovary might also become the target of SARS-CoV-2.

Given the possibility that there are other viruses that can affect the ovarian reserve, most of the publications have focused on pelvic inflammation as a cause of infertility due to tuberculosis and not directly as a cause of premature ovarian failure. Decreased ovarian reserve, with lower AMH levels and lower antral follicle counts, has been observed, but the underlying mechanisms are unclear [4]. Hypothetically, medical treatment for chronic infections could be correlated with a decrease in ovarian reserve, since it is likely that interferon and ribavirin affect the ovarian reserve of treated patients, with a variation in AMH levels over a wide range. The proportion of women treated [5].

Regarding HIV, a direct link between HIV infection and diminished ovarian reserve remains to be established, however, using AMH serum as a proxy, different groups found both higher [6] and lower [7,8] AMH levels in women living with the virus. It has been described that viral load may be related to a decrease in serum AMH levels and that an increase in CD4+ cell count is directly related to AMH levels [8]. Such inconsistencies make it difficult to confirm whether there is a correlation between HIV infection and ovarian reserve.

Over the last decade, female reproductive health has become increasingly important, and attention has been called globally to the effects of SARS-CoV-2 on the reproductive system. Clinical evidence is needed to confirm whether SARS-CoV-2 viral infection causes endocrine disruption and ovarian damage in women of childbearing age [9]. Antimüllerian hormone (AMH) is a glycoprotein produced by the granulosa cells of the antral and preantral follicles of the ovary in women. Its circulating levels have been proposed as a predictor of the ovarian response to ovarian stimulation and as a measure of the ovarian follicular reserve [10]. Unlike other reproductive hormones, AMH levels are not influenced by the state of the menstrual cycle. And are considered today as the measure of choice for estimating ovarian reserve.

Since it was described the presence of receptors of the virus in the ovary [11] further studies on the reproductive involvement of coronavirus infection were warranted, particularly with recovered patients. The objective of our work was to assess whether, in women who have passed the disease, there was a variation in the ovarian reserve through the determination of AMH levels before and after the illness.

Methods

Prospective and observational multicentre analysis to assess whether there are variations in AMH levels, as a marker of ovarian reserve, in women who have overcome a SARS-CoV-2 infection. Women with positive serology (IgG positive) for the disease and who had previous determinations of antimüllerian hormone (AMH) were identified; they were contacted by telephone and authorization was requested for a new determination of the hormone. The study was approved by an Institutional Review Board (2007-MADR-052-AR) and all women provided written informed consent.

The study period included May-June 2020, and we included all women with a positive serology for SARS-CoV-2 (IgG positive) and a previous AMH determination of no more than 6 months. Once the study population was identified, a new determination of AMH was performed to assess whether the infection had affected hormone levels, and therefore, ovarian reserve. Both determinations were performed with the Elecsys® device (AMH, Roche Diagnostics). Finally, study participants were stratified into two study groups according to their prior AMH levels: low ovarian reserve (AMH < 1 ng/mL) and normal/high ovarian reserve (AMH ≥ 1 ng/mL).

To minimize bias, each woman acted as self-control before and after the disease. Patients underwent ovarian stimulation using standardized protocols based on age, antral follicle count (AFC), antimullerian hormone (AMH), and body mass index (BMI). When 3 or more follicles reached 18 mm in diameter, ovulation trigger was performed with r-hCG (Ovitrelle®, Merck) or GnRH analog (Decapeptyl®, Ipsen Pharma) [12]. Intracytoplasmic sperm injection was performed in all cases, and fertilization was assessed 16–18 h after microinjection.

The main variable of the study was the change in AMH levels in women with IgG positive for SARS-CoV-2 infection before and after the disease. Other response variables were the comparative analysis related to the doses of administered gonadotropins, days of stimulation, number of retrieved, and number of mature oocytes in the two cycles performed (pre- and post-illness). Age (years) was identified as a control variable.

The database was rigorously defined with the variables intended to be analyzed based on the proposed objectives. Regarding the analysis of homogeneity, and, although the inclusion and design criteria tended to preserve the homogeneity of the study groups, it was advisable to ensure that there were no extraneous population effects. Therefore, the control variables were contrasted to assess the comparability between groups. Categorical variables were compared using a Chi-square test and for qualitative variables an ANOVA test. Statistical analyses were performed using the Statistical Package for Social Sciences 19.0 (IBM Corporation, Armonk, NY, USA).

Results

In this study 46 patients were included; 16 women were diagnosed with a low ovarian reserve (AMH<1 ng/ml) with an average year of 38.6 years, while 30 were identified as a normal ovarian reserve, with an average age of 34.7 years. In general, the data obtained did not show a significant variation in AMH levels before and after infection by SARS-CoV-2 (1.73 ng/ml *vs.* 1.61 ng/ml) respectively. However, when these differences were analyzed according to the study groups (Table 1), the data suggested that in women with a normal ovarian reserve, the average level of AMH before the infection was 4.6 ng/ml, while after the infection decreased to 3.1 ng/ml. For women with low ovarian reserve, the AMH was 0.8 ng/ml before the infection and was maintained at similar values after the infection AMH = 0.7 ng/ml.

According to the follicle antral count, the results were

Table 1: Variation in AMH levels after infection with SARS-CoV-2.

	Pre-SARS-CoV-2	Post-SARS-CoV-2	*p* - value
General (*n* = 46)	1.73 ng/ml	1.61 ng/ml	0.789
Normo-high ovarian reserve (AMH ≥ 1 ng/ml)	4.6 ng/ml	3.1 ng/ml	0.125
Low ovarian reserve (AMH < 1 ng/ml)	0.8 ng/ml	0.7 ng/ml	0.654

similar for both study groups before and after the infection. For a normal ovarian reserve with AMH values ≥ 1 ng/ml, women passed from 13 follicles to 11.5 follicles after having overcome the infection; however, in those cases of low ovarian reserve (AMH < 1 ng/ml), the values obtained went from 8.0 to 7.0 follicles respectively.

The results of the ovarian response are presented in Table 2. At this point, it should be noted that the post-infection treatment was carried out in no more than 3 months. It was observed that both the dose of gonadotropins administered, and the days of stimulation did not vary with respect to the treatment before and after the SARS-CoV-2 infection. Regarding the number of oocytes recovered and mature oocytes in each of the treatments performed, the numbers were very similar before and after the disease; these data were maintained when the fertilization rate was analyzed, in which hardly any differences were found in the two consecutive treatment cycles, only interrupted by the disease.

Table 2: Results of the cycle after infection with SARS-CoV-2.

	Pre-SARS-CoV-2	Post-SARS-CoV-2	*p* - value
Doses of gonadotropins (IU)	2053 ± 125	2035 ± 95	0.768
Days of stimulation	11.0 ± 1.1	10.7 ± 0.9	0.902
Retrieved oocytes	11.0 ± 1.5	10.8 ± 1.2	0.875
Metaphase II oocytes	9.3 ± 0.8	8.3 ± 1.0	0.413
Fertilization rate	77.4%	74.7%	0.369

Discussion

Currently, SARS-CoV-2 infection continues to raise many questions regarding short and long-term effects on general health. Clinical manifestations are very heterogeneous and affect many different organs.

During the last decade, women's reproductive health has become increasingly important and since the outbreak of the pandemic, the focus has been on the effects of the SARS-CoV-2 on the ovarian function of women of reproductive age. Data related to the effect of the virus on fertility are scarce. As we know, SARS-CoV-2 attacks human cells by binding the S protein of the virus the ACE2 receptor; in the ovary, ACE2 plays a key role in the response to gonadotropins, regulation of steroidogenesis, angiogenesis, and follicular deterioration [13]. Since the presence of ACE2 receptors in human ovaries has been described and angiotensin has been detected in measurable amounts in follicular fluid, a possible impact of infection on ovarian function could not be ruled out [14]. Although no differences were observed in the concentration of sexual hormones in patients affected by the disease with respect to the controls, it was detected that some women had unusually high concentrations of FSH and LH in the early follicular phase. In a situation of intense stress, ovarian function is usually suppressed to guarantee the functioning of other essential organs, hence the existence of anovulation episodes associated with many acute diseases [9]. Therefore, considering that the changes in hormone concentrations were temporary and transient, it was possible to assume that SARS-CoV-2 infection seemed to have little impact on ovarian response.

From a general point of view, and based on our own results, we could assume that SARS-CoV-2 infection did not affect ovarian reserve in a population of asymptomatic women who underwent Assisted Reproduction treatment, as we did not find significant differences in the AMH levels before and after having passed the disease. These results coincide with those of other studies [14-16]. That suggested that neither having passed the disease nor the mRNA vaccine had short-term detrimental effects on ovarian reserve.

As previously discussed, patients with a decreased ovarian reserve and AMH values less than 1 ng/ml were older (38.6 years) than women with a normal ovarian reserve and AMH values greater than 1 ng/ml (34.7 years). In addition, we also observed that AMH levels did not change in both normal and low ovarian reserve conditions. This circumstance could be explained by the fact that in cases of low ovarian reserve, which is known are characteristic of older patients, there could be a more pronounced decrease in primordial follicles in the context of a supposedly older ovary, and this could have potentiated the impact of the infection; however, we did not observe differences beyond those of the patient's ovarian status. Although the quantity and quality of information on the effect of the SARS-CoV-2 infection and/or the vaccine on fertility are incomplete and fragmentary, the literature available to date is positive and encouraging. In summary, our results showed that in patients who underwent an Assisted Reproductive treatment, the AMH levels before and after the disease, and that this finding was also consistent after analyzing differences by age groups [16]. The AMH differences between two consecutive determinations were not significantly different between patients positive and negative for the illness [13].

Despite these positive results, the effect of SARS-CoV-2 infection on the female reproductive system has not been fully elucidated. Preliminary data suggested potential ovarian injury during the active infection process, which could lead to a deleterious effect of SARS-CoV-2 on ovarian reserve and reproductive endocrine function [2]. However, our results not only showed stability in AMH levels regardless of having passed the disease but also did not present significant differences in terms of doses of administered gonadotropins and days of ovarian stimulation. Finally, the quality and quantity of retrieved oocytes were similar in both treatments, as demonstrated by the fact that the proportion of mature oocytes and the fertilization rate were quite similar before and after the virus infection.

The evaluation of ovarian reserve in the context of COVID-19 using the determination of AMH as an approximation factor has reported contradictory results.

Li, et al. found no difference in AMH levels when comparing women who contracted COVID-19 with controls [9] and Bentov, et al. found no impact of SARS-CoV-2 infection and/or COVID-19 vaccination on ovarian function [17]. On the other hand, Ding, et al. found lower serum AMH levels in women hospitalized due to COVID-19 compared to matched controls [18]. In general, it appears that infection and vaccination do not affect ovarian reserve; however, the full extent of its influence on ovarian reserve and the ramifications for fertility may not yet be apparent. In addition, the rapid mutability of the virus may introduce variants with different affinities for the receptors that result in a greater impact on the ovary.

In summary, the absence of significant interpersonal changes in plasmatic AMH levels before and after SARS-CoV-2 infection, and the fact that hormonal concentrations also remained stable depending on age allowed us to conclude that SARS-CoV-2 infection did not negatively affect the ovarian reserve.

Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Mara Campitiello, María Cruz, Cristina González-Ravina, and Alberto Pacheco. The first draft of the manuscript was written by Mara Campitiello and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective cohort study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board at IVIRMA Global and the Spanish Clinical Research Ethics Committee approved this study.

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