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The Impact of COVID 19 Pandemic on Pregnancy Outcomes of ART Cycles

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Abstract

The aim was to detect the rate of Covid-19 positivity in asymptomatic infertile patients admitted to ART Department during the pandemic and also investigated the effect of the Covid-19 pandemic on early pregnancy loss rates and pregnancy outcomes of ART cycles in Turkey. This cross-sectional study presents an analysis of prospective data collected at a single tertiary hospital. 346 couples were screened for Covid -19 PCR positivity during the pandemic. 185 fresh, non-donor, IVF pregnancies were reviewed in periods of 1 year before and after the Covid-19 pandemic. A total of 346 asymptomatic infertile couples were screened for Covid-19 positivity upon admission to the hospital for infertility treatment during the pandemic and Covid-19 positivity was defined as 2.1 %. The groups were compared in terms of clinical and laboratory parameters; there were significant differences in peak E2 levels, gonadotropin duration day, gonadotrophin dose, endometrium thickness, and >14 mm follicle count on HCG trigger day. There were no significant differences in the oocyte, M2, 2PN number, the total number of the embryos between the groups. When the study and control groups were compared in terms of early pregnancy losses the results were found to be similar. Although there was a difference in the drug requirement and response required for ovarian hyperstimulation, no difference was found in the number of oocytes collected, the number of M2, and the number of embryos obtained. In our study, this situation did not affect the rates of early pregnancy loss.

Keywords: Covid-19, Early pregnancy loss, IVF, Pandemic

Introduction

The covid pandemic was declared by World Health Organization on March 11, 2020, due to the common Covid-19 infection all over the world. Since then this novel coronavirus has spread throughout the world (1). All over the world and as well as our country, nonurgent procedures and treatments have been stopped at the beginning of the pandemic with the recommendations of health authorities and associations (2). The measures that were taken to prevent the spread of the infection were applied in the field of reproductive health as well as in all areas of health (3). In this period when the pandemic was brought under control, the need for other health services had gradually increased (4). Therefore, it is inevitable that other health services will start. Health societies all over the world have prepared guidelines to provide healthcare for patients with and without Covid-19 within the same system In this process, in our country, all assisted reproductive treatment has been started again under the attention to prevent the patients and staff across the Covid-19 (3-6).

With the restart of fertility care services around the world, it has become important for healthcare providers to be aware of the impact of Covid-19 on male and female reproductive cells and tissues. There are still many unknowns about Covid-19 infection. It is not yet known whether human embryos will be affected by Covid-19 or other coronaviruses in IVF treatment. In the few studies available, it has been found that many cells that develop human embryos express coronavirus receptors and also contain the necessary mechanism for viral internalization and replication (7). Therefore, it is stated that pregnancy should be avoided in a woman with symptoms of Covid-19. Also, the relationship of the new coronavirus infection with the human male and female reproductive systems is not yet fully known. Current data show that the female reproductive system can be protected from viral infection (8). It has been determined that the presence of ACE2 protein, which is the main receptor for the entry of the Covid-19 virus, has been identified in tissues taken from a small patient group, but the virus could not be identified (9). Similarly, ACE2 has been detected in adult Leydig cells in the testis of males and data are showing that ACE2 plays a role in spermatogenesis. Studies are showing male reproductive system damage after Covid-19 infection (10). Yang et al. reported that there were pathological changes as mild inflammatory infiltrates in testis with Covid 19 infected man (11).

ACE2 enzyme is intensely expressed in the ovaries as in many tissues, but the available evidence suggests that the female genital tract is unlikely a route of Covid-19 transmission. Aslan et al. reported that all over genital tract samples were negative in confirmed Covid-19 pregnant women (12). Qiu et al. analyzed vaginal samples with severe Covid-19 infected women, all samples tested negative for the virus (13). In addition, a systematic review of the case series among other parameters showed no presence of Covid-19 in vaginal mucosa and breast milk in all 28 tested pregnant women (14).

This study aimed to detect the rate of Covid-19 positivity in asymptomatic infertile patients admitted to ART Department during the pandemic and also investigated the effect of Covid-

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19 pandemic on early pregnancy loss rates and pregnancy outcomes of ART cycles in Turkey.

Materials and Methods

A retrospective cross-sectional study was conducted at the Department of Assisted Reproductive Technology of Ankara City Hospital. Institutional ethical approval was obtained (E1 20-586) and written informed consent was taken from the couples involved in this study. Firstly 346 couples were screened for Covid -19 PCR positivity during the pandemic. Then outcomes of 185 fresh, non-donor, IVF pregnancies were reviewed in periods of 1 year before and during the Covid-19 pandemic. Clinical details of all treatment cycles were retrospectively collected into a computerized database.

For patients in the study group (n:75); the management of the patients who are admitted for examination and treatment should have been resumed according to the Covid- 19 ART algorithm (Figure 1). The patients who admitted infertility treatment during the Covid-19 pandemic are evaluated in the triage section. The risk group is defined by filling the risk assessment form: 1. risk-free case 2. suspicious case 3. confirmed case after risk evaluation. Patients with risk factors and showing symptoms of the disease were not admitted to the ART treatment program and their treatment was delayed until the test results are clear. First of all the patients who had no PCR test positivity were accepted for infertility treatment. The patient and the partner were informed about Covid-19 infection and their treatment was completed after obtaining their consent. In this process, since the Covid-19 infection could be asymptomatic at a rate of 80%, absolute use of personnel protective equipment (PPE) was important for both the patient and the health personnel. Secondly, patients needed to be evaluated again in terms of infection symptoms, risk factors, and PCR test positivity before oocyte pick-up.

For patients in the control group (n:110); The patients who were admitted to the health care facility with child requests before the Covid-19 pandemic were included in the group. The exclusion criteria were a history of recurrent pregnancy loss, any significant systemic disease or endocrine or metabolic disorder, or concomitant medication interfering with the purposes of the study. Clinical and laboratory characteristics of patients were reported retrospectively. Pregnancy results of all patients were monitored from hospital records. Clinical pregnancy, miscarriage, and ongoing pregnancy rate were reported.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS.22, IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp.). Visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) were used to determine the normality of distribution. As the data were not normally distributed, medians and interquartile range values were used for descriptive analysis. Additionally, the Mann-Whitney U test was conducted to compare the median values and the chi-square test was used to compare categorical variables among the groups. A two-tailed P value < 0.05 was regarded as statistically significant.

Results

Firstly; a total of 346 asymptomatic infertile couples were screened for Covid-19 positivity upon admission to the hospital for infertility treatment during the pandemic and Covid-19 positivity was defined as 2.1 %, 8 female and 7 male patients were evaluated as PCR positive. Secondly; 185 fresh, non-donor, IVF pregnancies were reviewed in periods of 1 year before and during the Covid-19 pandemic. There was no difference between basal parameters such as age, infertility indication, BMI, ovarian reserve, smoking for both groups. The study (IVF pregnancy during the Covid pandemic) and control (IVF pregnancy before the Covid pandemic) groups were compared in terms of clinical and laboratory parameters; there were significant differences in peak E2 levels, gonadotropin duration day, gonadotrophin dose, endometrium thickness, and >14 mm follicle count on HCG trigger day (p 0.001, 0.001, 0.001, 0.001, 0.003, respectively). There were no significant differences in the oocyte, M2, 2PN number, the total number of the embryos between the groups (p:0.051; 0.12; 0.71; 0.87, respectively). When the study and control groups were compared in terms of early pregnancy losses the results were found to be similar (25,3 vs 26.4% respectively; p: 0,875). Four pregnant patients who had Covid-19 infection during pregnancy are still being followed up in group 1. Clinical and laboratory characteristics of patients were shown in Tables 1 and 2.

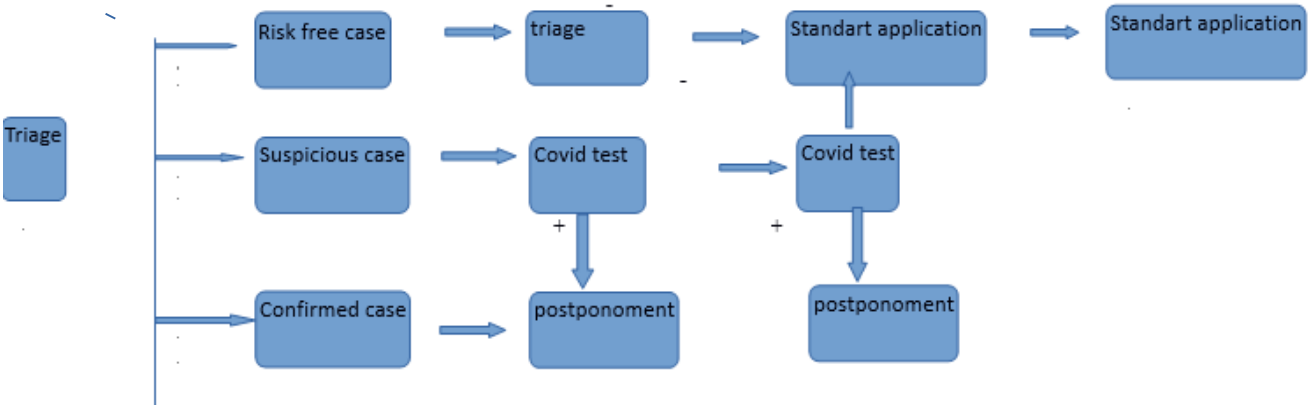

Figure 1. Infertility and IVF patients' management algorithm under Covid 19 pandemic

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Table 1. Clinical and laboratory caracteristics of patients

	Group 1 during the Covid19 pandemic (n=75)	**Group 2 before the Covid 19 pandemic (n=110)**	***p***
Age (year) median (min-max)	30,93±4,90	31 (19-44)	*0,539*
BMI mean + std	25,48±3,72	25,4±4,37	*0,962*
Smoking **Non-smoker n (%)** **Less than 1 pack per day n(%)** **More than 1 pack per day n(%)**	 46 (93,9) 2 (4,1) 1 (2)	 104 (94,5) 6 (5,5) 0 (0)	*0,305*
FSH IU/L	7,7 (0,3-15)	6,9 (1,4-15)	*0,076*
E2 pg/ml	40 (11-176)	42 (13-294)	*0,671*
AMH ng/ml	2,41 (0,2-9,0)	2,3 (0,03-18)	*0,979*
Antral Follicle Count	12 (3-31)	13 (1-30)	*0,466*
Initial Gonadotropin Dose IU	187 (112-300)	225 (112-375)	*0,045*
Peak E2 pg/ml	1198,5 (308-5548)	1897 (379-5497)	*<0,001*
Gonadotropin Duration day	9 (6-13)	9,5 (7-13)	*<0,001*
Total gonadotropine dose IU	1859,00±582,97	2334,7±786,9	*0,001*
HCG trigger day Endometrium mm	9,5 (6-14,6)	10,45 (6,2-15)	*0,001*
HCG trigger day >14mm Follicle	6 (1-15)	7 (1-19)	*0,003*
Total number of oocyt	7 (2-22)	9 (2-22)	*0,051*
M2	6 (1-22)	7 (1-20)	*0,123*
PN	4 (1-15)	4 (1-11)	*0,710*
Total number of embryo	4 (1-14)	4 (1-11)	*0,873*
1 ET n (%) **2 ET n (%)**	57 (76,0) 18 (24,0)	73 (66,4) 37 (33,6)	*0,707*
Good Quality Embryo n(%) **Blastocyst n (%)**	42 (56,0) 33 (44,0)	70 (63,6) 40 (36,4)	*0,237*
Embryo transfer day	3 (1-5)	3 (2-5)	*0,874*
Male factor infertility n (%) **Unexplained infertility n (%)** **Poor ovarian reserve n (%)** **Other factor n (%)**	29 (38,7) 23 (30,7) 19 (25,3) 4 (5,3)	60 (54,5) 32 (29,1) 13 (11,8) 6 (4,5)	*0,068*

P<0.05 is significant

Table 2. Pregnancy Outcomes

	Group 1 during the Covid 19 pandemic (n=75) (1 patient out of follow-up)	**Group 2 before the Covid 19 pandemic (n=110)**	***p***
Early pregnancy loss/ clinical pregnancy n (%) **Ongoing pregnancy/ clinical pregnancy n (%)**	19 (25,3) 56 (74,7)	29 (26,4) 81 (73,6)	*0,875*

P<0.05 is significant

Discussion

With the return to normal daily practice, all assisted reproductive treatment started again under the attention to prevent the patients and staff across the Covid-19 according to Covid 19 guidelines (1). One of the challenges from the beginning of the pandemic has been to find reliable diagnostic tests for this new virus, with results in a short time. The oropharyngeal taken under appropriate conditions swab PCR test for Covid-19 is the most accurate and reliable test for diagnosing Covid-19. Regardless of the purpose of the PCR test, it is necessary to optimize the reagent and PCR parameters to be used for each gene region. Therefore, many tests have been developed until this time and the false-negative rate for PCR testing is highly variable. Due to the nature of the PCR test, the PCR tests of some cases will be negative even if the entire population is screened (15). Even if PCR was performed on all of the patients who applied at the triage stage in our clinic, considering the possibility of false-negative results, a certain proportion of patients should not have been detected although they were positive.

In the first part of the study, 356 asymptomatic infertile couples were screened for Covid-19 positivity upon admission to the hospital for infertility treatment during the pandemic, and 8 female and 7 male infertility patients were evaluated as PCR positive during the pandemic. These couples were excluded from the ART program. Covid-19 positivity was defined as 2.1

% in our clinic. Our study is the first study to report this rate in the infertile patient population. Similarly, Tanacan et al. found the covid 19 test positivity as 1.4% in asymptomatic pregnant women admitted to hospital in their study (16).

In the second part of the present study, we evaluated early pregnancy outcomes of IVF patients. Although there are no reports of the presence of the Covid-19 virus in the female reproductive system, vaginal secretions, amniotic fluid or peritoneal fluid, Covid-19 infecting sperm or egg cells and staying silent here may create risky situations for possible embryo formation (17). It is not known whether human embryos will also be affected by Covid-19 or other coronaviruses in IVF treatment (18). Studies showing the opposite have also been reported in the literature. In the case reported by Demirel et al., they could not detect a virus in the follicular fluid aspirate of a covid-positive patient (19). Health authorities all over the world recommend canceling the treatment in patients who are still in the oocyte stimulation stage and who have symptoms of Covid-19 who have not yet received treatment due to lack of information, uncertainty, and possible harms. We did the same in our clinic. In addition, it is recommended that the treatment be canceled in patients who are still in the oocyte stimulation phase and who have symptoms of Covid-19 who have not yet received treatment. It has been reported that embryo transfer should not be performed in patients who develop symptoms after oocyte collection similarly as in our clinic. As there may be asymptomatic patients, screening for Covid-19 is also among the recommendations to prevent potential threats to developing embryos (ASRM, 2020; British Fertility Society, 2020) (3,4).

We investigated the effect of the Covid-19 pandemic on early pregnancy loss rates and pregnancy outcomes of IVF patients. As a result; although there was a difference in the drug requirement and response required for ovarian hyperstimulation, no difference was found in the number of oocytes collected, the number of M2, and the number of embryos obtained. In our study, this situation did not affect the rates of early pregnancy loss. The present study is the first study in the literature to our knowledge. On the other hand, limited studies are available to investigate the effect of Covid-19 on pregnancy outcomes with infected pregnant women. Generally, pregnant women with Covid-19 pneumonia showed a similar pattern of clinical characteristics to non-pregnant adult patients. There is no information showing that pregnant women are more susceptible to Covid-19. There is no evidence that it causes intrauterine infection and congenital infection, but it is difficult to decide on this issue due to the low number of cases (20). Although the vertical transmission rate and the result of Covid-19 in the first trimester are not known clearly, potentially receptor expression of Covid-19 in the placenta and decidual cells could play an important role in promoting the transmission of Covid-19. Wong et al in their study; noted that four out of seven (57%) women presented during first-trimester spontaneous miscarriage, likely attributed to hypoxia caused by SARS-related acute respiratory illness (21). When we compare the rate of early pregnancy loss in our study we found the rate of early pregnancy loss similar for both groups. In addition, we cannot give a live birth rate because they live birth period of pregnant women in the covid period has not yet been completed. The limitation of this study was retrospective design, in addition, we cannot give a live birth rate because they live birth period of pregnant women in the covid period has not yet been completed and there was no difference in ongoing pregnancy and abortion rate.

Ethical approval

All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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The study received no funding.

Conflict of interest

The authors declare no conflict of interest.

Authors' contribution

All authors of this study have a complete contribution for data collection, data analyses, and manuscript writing.

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