

The Effect of COVID-19 Pandemic on Outcome of Assisted Reproductive Technology: A Report from a Single Infertility Center

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Abstract

Objective: COVID-19 pandemic has affected all aspects of human life including social, economic, healthy behaviors and even individual relationships. This study aimed to investigate the effect of corona virus outbreak on assisted reproductive technology (ART) outcome.

Materials and methods: In this retrospective and prospective cohort, 260 ART cycles of ovum pick up (OPU), fresh embryo transfer (ET) and frozen embryo transfer (FET) were evaluated in 223 women (from December 2019 to February 2020) and during COVID-19 outbreak (February and July 2020) in an infertility center. Primary and secondary outcomes of ART cycles including chemical and clinical pregnancy rate were evaluated.

Results: The mean±SD (standard deviation) age of women was 34.17±6.56 years. Chemical and clinical pregnancy rates were 23.91% (33/138) per embryo transfer and 75.8% (25/33) per positive pregnancy test, respectively while ongoing pregnancy was seen only in 69.7% (23/33) of those with positive pregnancy test. Spontaneous abortion rate was 15.15% (5/33) per laboratory pregnancy. COVID-19 symptoms were reported in 2.83% and 15.38% of women during and after ART cycles, respectively.

Conclusion: It seems that COVID-19 pandemic has not negative effect on outcome of ART cycles except for cancelation rate due to COVID-19 that increased at the beginning of COVID-19 outbreak as it was unknown at that time and awareness was limited.

Keywords: COVID-19; Pandemics; Assisted Reproductive Technique; Infertility

Introduction

COVID-19 pandemic is an unexpected global

condition which is significantly changing our daily life and perception (1). COVID-19 pandemic has raised hospitalization in the world and also have some maternal and fetal effects. Although, its effect on IVF (in vitro fertilization) cycles is uncertain. Human reproductive societies suggested suspension

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of new (assisted reproductive technique) ART cycles initiation and cancellation of all fresh or freeze embryo transfer (2, 3), continue to care for patients who are currently in cycle or require urgent stimulation and cryopreservation (2, 3), suspend elective surgeries and no urgent diagnostic procedure (1). Countries have adopted their own timing of risk reduction strategies (4). Living with uncertainty, has led most countries to cancel all ART/IVF cycles, except for fertility preservation in patients exposed to gonado toxic chemo or radiotherapy (5).

During the past nine months from the beginning of COVID-19 outbreak in Wuhan, China (6) up to now (April 8, 2021), 134,190,375 patients have been infected with SARS-CoV-2 virus that caused 2,907,652 deaths worldwide. In Iran, COVID-19 outbreak was reported first in 20 February 2020 and up to now 2,006,934 cases of disease have been identified that caused 63,884 deaths (7).

In addition to huge number of deaths caused by COVID-19 worldwide, it has affected different aspects of life and health extensively and yet many effect of this disease remained unknown. One of these aspects is human reproductive outcome that no mass knowledge is known about the effect of corona virus on it. Social limitations due to COVID-19 have affected and reduced number of ART cycles like other medical services during the outbreak. However, the effect of corona virus on reproductive function of male and females are not known well and scarce information are contradictory.

Segars et al data suggest that the female reproductive system may be spared from viral infection (8). Male fertility may be diminished for 72 – 90 days following COVID -19 due to decreased sperm concentration and motility (9, 10).

Gametes obtained from patients with (human immunodeficiency virus) HIV or (hepatitis B virus) HBV infection must be treated with special precautions (11), these anticipations are not recommended currently for SARS –COV-2, due to lack of information about sexual or blood transmission (2).

Long term locked down ART might have detrimental effects on society and infertile patients, especially low prognosis patients who constitute 30-50% of patients seeking ART (12). Generally 1.5 million IVF cycles are done annually in the world, and 400000 babies born resulting from IVF (13), which is 0.3% of annually living birth rate (13). Due to undetermined effect of COVID -19 pandemic on fertility and infertility treatment, this study aimed

to investigate the outcome of ART cycles before and during COVID -19 pandemic.

Materials and methods

In this retrospective and prospective cohort study infertile women undergoing ART cycle in Vali-e-Asr Infertility Center before (December 2019 and January 2020) and during (15 February to 15 March and July 2020) COVID -19 outbreak were evaluated. All ART cycles including, ovum pick up (OPU), fresh embryo transfer (ET), and frozen embryo transfer (FET) during the mentioned period were included. Our evaluation consisted of two parts; first part (before pandemic) included all ART cycles performed in December 2019 and January 2020 as duration before COVID-19 outbreak, and second part (during pandemic) included all ART cycles performed from 15-February to 15 March and July 2020 as duration of the corona outbreak. However, due to Iranian New Year holidays from March 20th to April 3rd and then due to COVID-19 pandemic lockdown, up to July 2020, ART cycles were stopped.

Before inclusion of women in ART cycle, they received consult for symptoms of COVID-19 and if they had positive clinical symptoms were excluded from ART treatment. However, one of women developed COVID-19 symptom during the course of ART cycle but completed the cycle.

Primary outcomes were laboratory and clinical pregnancy rate and secondary outcomes were ongoing pregnancy, abortion, ectopic pregnancy and fetal anomaly. ART complications, presences of COVID -19 symptoms during and after ART cycles, hospital admission and cycle cancellation rate as well as sperm parameters of male partner were recorded also. These data were obtained from medical records' and by telephone interview with the patient.

The study protocol was approved by ethics committee of Tehran University of Medical Sciences with number IR.TUMS.VCR.REC.1399.426 and all patients gave written informed consent before enrollment.

Statistical Analysis: Numerical variables were presented as mean and standard deviation (SD) and categorical variables were shown as number and percentage. Data analysis was performed using descriptive statistics. Data with normal distribution were compared using independent sample t-test and categorical data by Chi square test. SPSS software was used for data analysis and p_ value less than 0.05 was considered significant.

Results

During the study period 260 cycles from 223 women were evaluated. Mean±SD age of studied women was 34.17±6.56 years. Of all cycles, five were canceled before and three during pandemic. Demographic characteristics of women underwent ART have been presented in Table 1.

Table 1: Demographic information of participants

Variable	n	Mean ±SD
Age (year)	223	34.17±6.56
BMI (kg/m ²)	201	26.44 ±4.32
Duration of infertility (year)	210	5.40±4.45
Duration of Cycle (days)	260	12.03±3.08
AMH level (ng/ml)	217	3.86±4.25
Picked up oocyte (N)	155	5.20±5.28
Oocyte in metaphase 2 (N)	141	4.85± 4.88
2PN (N)	137	5.00±5.31
Sperm Count (million per ml semen)	130	38.77±26.58
Sperm with normal morphology (percent)	130	4.18±1.76
Sperm motility (percent)	130	49.08±17.64

BMI: body mass index, AMH: anti mullerian hormone, 2PN: 2 pronuclear

Primary outcome of ART cycles before and during COVID-19 pandemic has been shown in Figure 1.

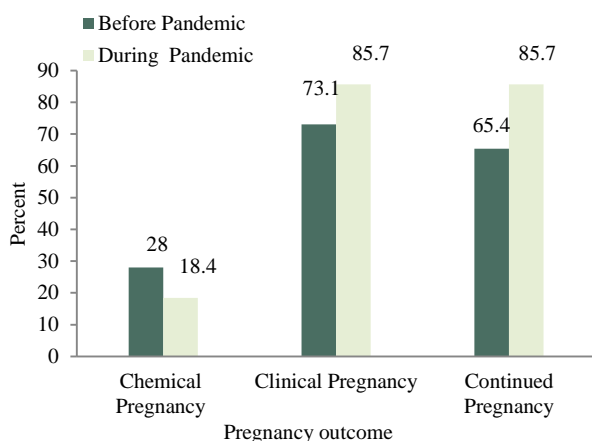


Figure 1: Outcome of ART cycles before and during COVID-19 pandemic

Characteristics of ART cycles have been shown in Table 2. Infertility was the most common indication for ART in the study population. Laboratory pregnancy rate was 23.91% per embryo transfer (33/138) (including FET and ET before and during corona pandemic) and clinical pregnancy rate was 75.8% per laboratory pregnancy (25/33) (Table 3). Continued pregnancy rate was 69.7% (23/33) per laboratory pregnancy. There was no significant

difference in laboratory and clinical pregnancy rate and spontaneous abortion between before and during corona pandemic ART cycles ($p>0.05$) (Figure 1). Eight cycles of 260 (3.07%) were canceled which five of them occurred before pandemic and three were during pandemic (Table 4).

Table 2: Type and cause of ART before and during COVID-19 pandemic

Variable	n (%)
Type of ART cycles	
OPU	122 (46.9)
FET	101 (38.8)
ET	37 (14.2)
Total	260 (100)
Cause of ART cycles	
Infertility	209 (94.6)
Fertility preservation	12 (5.4)
Total	221 (100)
Cause of infertility	
Male Factor	57 (27.3)
Female Factor	77 (36.8)
Both Factor	51 (24.4)
Unexplained	24 (11.5)
Total	209 (100)

ART: assisted reproductive technology, OPU: ovum pick up, ET: fresh embryo transfer, FET: frozen embryo transfer

Only one of eight canceling (12.50%) was due to COVID – 19 pandemic. COVID-19 symptoms were reported in 7/247 (2.83%) and 38/247 of ART cycles (15.38%), during and after ART cycle, respectively (Table 4). Before pandemic, symptoms during ART cycle were reported in five cycles that two of them were OPU. Among the three transfers, only one positive chemical pregnancy test was observed. This pregnancy continued without any IVF complication, hospital admission or fetal anomaly. Before corona pandemic symptoms were reported after ART cycle in 25 women that 17 of them were embryo transfer that, chemical pregnancy was negative in 11 cycles and six of them had continued pregnancy. Among the six pregnant women, one was admitted in hospital due to other causes (except IVF complication or COVID-19 symptom). Fetal anomaly of brain cyst was observed in one fetus in anomaly scan.

During ART cycle, only one woman developed COVID-19 symptoms during corona pandemic that chemical pregnancy was negative for her. During corona pandemic, COVID-19 symptoms were observed after 13 ART cycles that of them eight were OPU.

Table 3: Primary and secondary outcomes of ART cycles before and during COVID-19 pandemic

Variable	Before Coronal Pandemic n (%)	During Corona Pandemic n (%)	P-value
Ongoing pregnancy (per chemical pregnancy in FET and ET without cancelled cycles)	17/26 (65.38)	6/7 (85.71)	0.39
Ectopic pregnancy (per laboratory pregnancy in all FET and ET cycles without cancelled cycles)	0/26 (0)	0/7 (0)	-
Fetal congenital anomaly (of all chemical pregnancy in FET and ET cycles without cancelled cycles)	2/26 (7.69)	1/7 (14.28)	0.42
Spontaneous abortion in (per chemical pregnancy in all FET and ET cycles without cancelled cycles)	4/26 (15.38)	1/7(14.28)	0.65
Type of fetal anomaly (those with chemical pregnancy including all FET, and ET cycles)	1/26 (3.84)		
Brain cyst		1/7 (14.28)	0.43
Club foot			
Fetal kyphosis	1/26 (3.84)		

ET: fresh embryo transfer, FET: frozen embryo transfer

Among five transfers, four were negative for pregnancy test and only one positive chemical pregnancy was observed. In this one pregnancy again pregnancy continued without any IVF complication, hospital admission and fetal anomaly.

Nineteen patients were admitted to hospital that three patients were admitted due to IVF complications and one patient due to respiratory symptoms after ART (Table 4). IVF complications are presented in Table 4. Spontaneous abortion was observed in 5/33 of positive pregnancies (15.15%) before and during pandemic. Primary and secondary ART outcomes including clinical pregnancy, continued pregnancy and spontaneous abortion rate

are presented in Table 3. Fetus anomaly was observed in 13.04% (3/23) of continued pregnancies. Also, there was no significant difference in sperm count, motility and morphology between before and during corona outbreak ($p>0.05$) (data not shown).

Discussion

In the current study the clinical pregnancy rate was 75.8% in infertile women. Primary outcomes of ART before and during COVID-19 pandemic was not significantly different Also, there was no significant difference in cycle canceling and hospital admission and IVF complication between before and during COVID-19 pandemic.

Table 4: ART complications and COVID-19 in the studied women before and during corona pandemic

Variable	Before Corona Pandemic n (%)	During Corona Pandemic n (%)	P-value
ART Complications (per cycle)			
No complication (all cycles)	142/155 (91.6)	84/92 (91.3)	0.51
OHSS (in OPU and ET cycles)	7/155 (4.5)	5/92 (5.4)	
Tuboovarian abscess (in OPU and ET cycles)	1/155 (0.6)	2/92 (2.2)	
Twin (FET and ET cycles)	5/155 (3.2)	1/92 (1.1)	
Cycle canceling (of all cycles of OPU, ET and FET)	5/155 (3.22)	3/92 (3.26)	0.64
Cause of canceling (all cycles of OPU, ET and FET)			
No response	2/155 (1.29)	1/92 (1.08)	0.37
Corona pandemic	0/155 (0)	1/92 (1.08)	
Other causes	3/155 (1.93)	1/92 (1.08)	
Hospital admission	12/155 (7.74)	7/92 (7.60)	0.59
Cause of admission (of all cycles)			
IVF complication	1/155 (0.64)	2/92 (2.17)	0.37
Acute respiratory symptoms	1/155 (0.64)	0/92 (0)	
Other causes	10/155 (6.45)	5/92 (5.43)	
Symptoms of COVID-19 during the cycle (all cycles of OPU, ET and FET)	6/155 (3.22)	1/92 (1.08)	0.28
Symptoms of COVID-19 after the cycle (all cycles of OPU, ET and FET)	25/155 (16.12)	13/92 (14.13)	0.43

OPU: ovum pick up, ET: fresh embryo transfer, FET: frozen embryo transfer, IVF: in vitro fertilization, ART: assisted reproductive technology, OHSS: ovarian hyperstimulation syndrome

However, the cause of cycle cancelling was significantly different between the two periods and cancelling due to COVID-19 was just during corona pandemic. Higher canceling rate of ART cycles at the beginning of outbreak may be due to unknown nature and characteristic of COVID-19 and unawareness and fear of patients about it.

In the current study, COVID-19 symptom during ART cycle was reported in six cycles before outbreak. The cause of such report may be due to recall bias because at that time yet outbreak has not been started or may be really symptom of corona and outbreak had been started but it was unknown yet.

As our patients in this condition according to European society of human reproduction and embryology (ESHRE) statement were patients with most priority (such as high maternal age, low ovarian reserve and fertility preservation) therefore, IVF success rate may be lower in the patients during corona pandemic although response rate in our study during corona outbreak was to somewhat higher than before outbreak. However, there was no similar study to compare.

The outbreak of novel corona virus disease (COVID-19) is a major epidemic threat all over the world (14). The disease has spread to almost all countries worldwide and the timeline to its complete removal is unpredictable and unknown.

According to American Society for reproductive Medicine (ASRM) and ESHRE statement in early phase of pandemic that recommended discontinuation of reproductive care except for the urgent cases during COVID-19 pandemic (15), we suspended ART cycles except for oncofertility and fertility preservation for patients exposed to chemo or radiotherapy.

However, considering unknown end of pandemic, recently, ESHRE, ASRM and the International Federation of Fertility Societies (IFFS) jointly released statement and highlighted the importance of continuing reproductive care during the current pandemic because it is necessary for the well-being of human and society and for maintaining birth rates at this time that many populations are experiencing declines due to the current pandemic mortality (15). In addition to the above points, this statement, highlighted the need for data gathering and research about reproductive outcome (spontaneous pregnancy or by ART) during COVID-19 pandemic (those conceived between March 1st and December 31st are encouraged) (15).

Considering above statement, ESHRE now is

gathering data regarding the outcome of pregnancies conceived by medically assisted reproduction (MAR) in women with confirmed diagnosis of COVID-19 (15). In this regard, our study is the first report in the world that releases the outcome of ART cycles during the early stages of COVID-19 pandemic (above highlighted date by joint committee) (first and second corona peak in Iran) (15).

Also, ESHRE is collecting data country by country regarding MAR/ART activity during the pandemic, to map whether and /or when they stopped reproductive care and when they restarted care (15). Regarding this point, our data can be presented to ESHRE as a report from Iran.

Regarding cryopreservation in cancer patients, National Transplant Centre (NTC) has recommended careful evaluation of the existing COVID-19 symptoms to avoid exposure of other patients as well as healthcare providers (16). Dellino et al study concluded that a screening for COVID-19 by serum antibodies or nasopharyngeal sample reverse transcription polymerase chain reaction (RT-PCR) should be mandatory in cancer patients undergoing fertility preservation to confirm their gametes are not infected by COVID-19 and can be processed for cryopreservation (17). Based on our COVID protocol, for all patient with positive symptom or sign of COVID -19 or positive CRP test, diagnostic test for COVID-19 was performed.

Few studies have evaluated the effect of COVID-19 on male and female reproductive organs and function. In Eisenberg study, SARS-CoV-2 was not identified in the semen by PCR and the study could not show any change in semen quality in male patients with COVID-19 infection (18).

Li et al have recently identified SARS – CoV-2 virus in semen of six male out of 38 positive patients (15.8%), including 4 of 15 (26.7%) in the acute stage of infection (19). Furthermore, two of 23 recovering patients (8.2%) were also positive for SARA-CoV-2 virus in the semen. (19) In the current study, semen samples were not assessed (by PCR) for COVID-19 infection because none of men had COVID-19 disease because according to our ward protocol both male and female candidate for IVF were screened for sign and symptoms of COVID-19 and if COVID-19 was positive, IVF would be canceled.

However, yet information about the effect of corona virus in female and male reproductive system is rare and needs to be completed.

Our study had some limitations. One of the

limitations is that information about COVID-19 symptoms was obtained by patients' self-report and this may cause recall bias. As, COVID-19 test was not performed, evaluating the effect of confirmed COVID-19 disease on ART and pregnancy outcome was not possible. The other limitation is that our hospital was referral center for COVID-19 and most of hospital wards were assigned to COVID patients and our center was in minimal activities for ART. Strength of our study is inclusion of large number of ART cycles.

Conclusion

The worldwide situation of COVID-19 pandemic is a special unpredictable condition. It seems that the virus will remain for unknown duration with human and may affect birth of over 100 million babies every year. Therefore, the reproductive implications of SARS-COV-2 should be further studied.

Current study did not show any negative effect of corona pandemic on ART cycles outcome and also no negative effect of COVID-19 on ART outcome as well. However, data gathering and future studies with greater sample size with evaluating reproductive outcome and live birth rate during COVID-19 outbreak with analysis of semen quality is required to increase our knowledge regarding the effect of this virus in reproductive organs.

All health care provider need to be alert, amend and adjust the treatment modalities according to the day to day changing information and published experience on the behavior of the new and unknown virus. ART specialists should be cautious, carefully monitor situation and share novel evidence to counsel patients.

Conflict of Interests

Authors have no conflict of interests.

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