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# Impact of Protocol Adjustments Due to the COVID-19 Pandemic on Infertility Treatment Outcomes



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## ABSTRACT

As a result of the COVID-19 pandemic, our centre made adjustments that reduced the number of patient visits, ultrasound scans, laboratory investigations, and face-to-face instructions. The objective of this study was to evaluate whether these changes had any effect on the pregnancy rate for patients undergoing infertility treatment. The primary outcome was clinical pregnancy rates from intrauterine insemination and frozen embryo transfer.

Clinical pregnancy rates were not statistically different between patients who underwent either procedure before and after the protocols were put in place. It is reassuring to know our pandemic protocol adjustments did not have a negative impact on infertility treatment outcomes.

Il n'y avait aucune différence statistique concernant le taux de grossesse clinique entre les patientes ayant subi l'une ou l'autre des interventions avant et après la mise en place des protocoles. Il est rassurant de constater que les changements de protocole imputables à la pandémie n'ont pas nui aux issues des traitements de l'infertilité.

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## RÉSUMÉ

En raison de la pandémie de COVID-19, notre centre a apporté des changements qui ont fait réduire le nombre de rendez-vous, d'échographies, d'analyses de laboratoire et d'instructions en personne pour les patientes. L'objectif de cette étude était d'évaluer si ces changements ont eu un effet quelconque sur le taux de grossesse des patientes en traitement de l'infertilité. Le critère de jugement principal était le taux de grossesse clinique associé à l'insémination intra-utérine ou au transfert d'embryons congelés.

**Keywords:** COVID-19; insemination, artificial; fertilization in vitro; embryo transfer; pregnancy outcomes

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## INTRODUCTION

The COVID-19 pandemic has affected many different domains of the health care system. In March 2020, the Canadian Fertility and Andrology Society, the American Society for Reproductive Medicine,<sup>1</sup> and the European Society for Human Reproduction and Embryology<sup>2</sup> recommended that assisted reproductive technology should stop to prevent overburdening health care systems. Infertility services were deemed 'nonessential.' Specifically in Ontario, to implement health and safety recommendations from the College of Physicians and Surgeons of Ontario guidelines and the Ministry of Health's COVID-19 operational requirements, multiple changes were made in treatment protocols and patient care at ONE Fertility, Burlington, Ontario, Canada.<sup>3</sup> Operational changes included fewer (1) in-person visits per patient, (2) ultrasound scans, (3) laboratory investigations, and (4) face-to-face instructions.

The purpose of this study was to evaluate and compare pregnancy rates among patients who had ovarian

stimulation with intrauterine insemination (IUI) and frozen embryo transfers (FET) cycles prior to the pandemic with those who were treated during the COVID-19 pandemic to understand if the temporary shutdown and newly developed protocols affected their overall success rates.

## **METHODS**

This is a retrospective cohort study with Hamilton integrated research ethics board approval (number 45999). Patients in this study who underwent IUI, in vitro fertilization (IVF), and FET at ONE Fertility were divided into two groups. The prepandemic group (IUI,  $n = 617$ ; IVF,  $n = 226$ ; and FET,  $n = 260$ ) were treated between June 2019 and December 2019. The pandemic group (IUI,  $n = 634$ ; IVF,  $n = 224$ ; and FET,  $n = 318$ ) were treated between June 2020 and December 2020. The primary outcome was clinical pregnancy rate, defined as the presence of a gestational sac and fetal heart at ultrasound examination at 6 to 7 weeks gestation. IVF cycles were freeze-all and were not included in the primary outcome. The secondary outcome was biochemical PR (positive serum  $\beta$ -hCG 12–14 days post-procedure) from IUI and FET, as well as number of eggs retrieved and fertilization rate from IVF cycles. Statistical analysis was performed and reported as mean  $\pm$  standard deviation of the mean. Where appropriate,  $t$  test and classical  $\chi^2$  calculations were conducted to determine significance ( $P < 0.05$ ) between groups. Protocol adjustments included the following.

### **Visits per Patient**

Prepandemic, every new patient referred to ONE Fertility underwent diagnostic cycle monitoring, involving a series of blood tests and ultrasounds to monitor one menstrual cycle. During the pandemic, diagnostic cycle monitoring and monitoring for intercourse cycles stopped.

### **Ultrasound Scans and Laboratory Investigations**

With the decrease in patient visits came the decrease in number of ultrasound scans for purpose of cycle monitoring.

### **Semen Collection**

Our study did not objectively collect data on whether men provided semen samples at home versus in clinic. If home collection was done, our patients provided their sperm sample within 1 hour of collection.

### **Face-to-Face Instructions**

This was substituted with online IVF e-modules created by the staff at ONE Fertility. These were sent to all patients by email and were required to be completed prior to starting an IVF cycle. All consents were obtained by phone and forms were signed electronically via DocuSign.

### **Intrauterine Insemination**

Before the pandemic, patients would call on cycle day 1. For letrozole + IUI, patients would be seen on cycle day 10 to monitor follicular growth by doing an ultrasound and estrogen/luteinizing hormone level. If the follicle size was  $<15$  mm, they would return in 2 days to have another ultrasound and hormone check. If the follicle was  $\geq 15$  mm they would return for ultrasound and blood work in 1 day. The clinic would schedule IUIs based on luteinizing hormone surge or Ovidrel trigger when the follicle was  $>20$  mm with good endometrial lining and appropriate estrogen level. For patients undergoing follicle stimulating hormone (FSH) + IUI, blood work and an ultrasound would be done on cycle days 3 and 8. The rest of the monitoring was like the letrozole + IUI cycle. During the pandemic, the number of visits were significantly reduced. For letrozole + IUI cycles, patients were seen for the first time on cycle day 10. Patients were provided information about their Ovidrel injection and/or progesterone suppository, ovulatory predictor kits (OPK), and collection cup for sperm sample. Patients were instructed to call the clinic once they had a positive OPK and take their Ovidrel. Their insemination would be scheduled for the following day. The morning of the IUI, a sperm sample would be collected in the collection cup provided and delivered to the clinic at body temperature within an hour of production. If there was no positive OPK by cycle day 20, the patient was instructed to call for an ultrasound and blood work. For FSH + IUI cycles, patients had blood work on cycle day 3 and were given all required information as above about the cycle on that visit. The next visit was cycle day 10. Once patients had a positive OPK, insemination was booked for the next day.

### **IVF**

Before the pandemic, patients would call on cycle day 1 and schedule cycle day 3 IVF start. Blood work and ultrasound would be done on cycle days 6, 7, and 8. Once follicles were  $\geq 15$  mm, patients would come in for daily bloodwork and ultrasound until they were ready for the Ovidrel trigger shot. During the pandemic, blood work and ultrasound were done on cycle days 3, 8, 10, and 12 and the trigger shot was administered at home.

### **FET**

We only included ovulatory protocols. These remained similar pre- and postpandemic. Prepandemic, patients called the clinic cycle day 1 and booked their bloodwork and ultrasound for cycle day 10. Continuous monitoring with blood work and ultrasound was done until transfer. During the pandemic, patients would attend clinic on cycle day 10 for bloodwork and an ultrasound, then were

**Table 1. Patient characteristics, IUI, IVF, and FET pre-pandemic versus pandemic**

Characteristic	Period; mean (SD)		P value (t test)
	Pre-pandemic	Pandemic	
IUI	n = 617	n = 634	
Age, y	31.2 (3.1)	35.0 (3.5)	0.19
BMI, kg/m <sup>2</sup>	24.2 (5.8)	26.3 (5.3)	0.32
AMH, pmol/L	18.9 (10.9)	14.1 (10.6)	0.55
Duration of infertility, y	1.4 (1.4)	1.6 (1.7)	0.95
No. of DFs	1.05 (0.4)	1.09 (0.5)	0.5
TMC	56.5 (41.7)	32.5 (38.1)	0.3
IVF	n = 226	n = 22	
Age, y	34.3 (6.2)	35.3 (4.6)	0.04 <sup>a</sup>
Total FSH dose	3694.8 (1824.0)	3642.1 (1728.7)	0.75
No. of stim days	10.0 (1.0)	12.0 (1.0)	0.53
Estrogen level	9511.2 (5365.6)	10949.3 (6369.3)	0.01 <sup>a</sup>
Day of hCG	13.5 (2.1)	13.4 (1.7)	0.62
No. retrieved	11.4 (6.7)	12.0 (7.1)	0.34
No. injected	8.3 (5.1)	9.5 (5.6)	0.02 <sup>a</sup>
Egg maturity	74.2 (20.7)	80.0 (16.0)	0.01 <sup>a</sup>
Fertilization rate	77.0 (26.3)	82.6 (20.5)	0.01 <sup>a</sup>
No. of cleaved embryos	6.4 (4.3)	7.5 (4.7)	0.01 <sup>a</sup>
Utilization (blast) rate	31.8 (65.4)	36.1 (22.6)	0.18
BMI, kg/m <sup>2</sup>	25.8 (5.8)	25.8 (5.3)	0.35
Duration of infertility, y	1.8 (1.3)	2.2 (1.6)	0.12
AMH, pmol/L	14.0 (10.3)	16.5 (12.6)	0.46
FET	n = 260	n = 318	
Age, y	36.2 (3.9)	35.8 (4.4)	0.19
BMI, kg/m <sup>2</sup>	25.8 (5.6)	26.0 (5.5)	0.93
AMH, pmol/L	18.2 (12.3)	18.9 (11.8)	0.39
Duration of infertility, y	1.6 (1.0)	1.9 (1.4)	0.07
No. of ETs	1.01 (0.14)	1.04 (0.19)	0.22

<sup>a</sup>Significant at  $P < 0.05$ .

AMH: anti-Müllerian hormone; BMI: body mass index; DF: dominant follicles >16 mm; ET: embryo transfer; FET: frozen embryo transfers; FSH: follicle stimulating hormone; hCG: human chorionic gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilization; TMC: total motile count.

instructed to do OPK testing at home. Once there was a positive result, the transfer would be scheduled.

## RESULTS

### Intrauterine Insemination

Patient characteristics including body mass index, duration of infertility, and the number of dominant follicles >16 mm were similar between the two groups (Table 1). The total motile count of sperm in the IUI sample was higher in the pre-pandemic group, with a mean of 56.5 compared with 32.5 M. Patients' anti-Müllerian hormone (AMH) levels were slightly higher in the pre-pandemic group, with a mean of 18.9 pmol/L compared with 14.1 pmol/L; however, this result was not statistically significant. The IUI clinical PR (pre-pandemic 12.3% vs. pandemic 11.7%) and biochemical

PR (pre-pandemic 14.4% vs. pandemic 13.1%) were not statistically different between the pre-pandemic and pandemic groups (Table 2).

### IVF

The average patient's age was slightly higher in the pandemic group, and they had higher estrogen levels on the day of booking for egg retrieval (Table 1). When comparing the two groups, there was higher egg maturity, a greater number of eggs injected with sperm, better fertilization rate, and a higher number of cleaved embryos in pandemic groups versus the pre-pandemic group. Despite this, the blastocyst development rate was not different between two groups. The AMH level in the pandemic group was slightly higher, at 16.5 pmol/L versus 14 pmol/L in the pre-pandemic group; however, these results were not

**Table 2. Comparison between IUI and FET outcomes prepandemic versus pandemic**

Description	Period; no (%)		$\chi^2$ P value <sup>a</sup>	$\chi^2$ Y P value <sup>b</sup>
	Prepandemic	Pandemic		
IUI	n = 617	n = 634		
GS on ultrasound	76 (12.3)	74 (11.7)	0.725	0.791
Positive FH	71 (11.5)	68 (10.7)	0.660	0.726
Positive $\beta$ -hCG	89 (14.4)	83 (13.1)	0.494	0.547
FET	n = 260	n = 318		
GS on ultrasound	113 (43.5)	149 (46.9)	0.725	—
Positive FH	81 (31.2)	108 (34.0)	0.660	—
Positive $\beta$ -hCG	113 (55.8)	183 (57.5)	0.668	—

<sup>a</sup>P value for  $\chi^2$  comparison.

<sup>b</sup>P value for  $\chi^2$  comparison with Yates correction.

$\beta$ -hCG: chorionic gonadotropin; FET: frozen embryo transfer; FH: fetal heart; GS: gestational sac; IUI: intrauterine insemination.

statistically significant. Additionally, the total FSH dose was similar in both groups.

### Frozen Embryo Transfer

Among patients who underwent FET, the baseline characteristics were similar in both groups (Table 1). The average age in the prepandemic group was 36.2 compared with 35.8. The AMH level and number of embryo transfers were also similar between both groups and not statistically significant. The clinical pregnancy rate (prepandemic 43.5% vs. pandemic 46.9%) and biochemical pregnancy rate (prepandemic 55.8% vs. pandemic 57.5%) were not statistically different between the prepandemic and pandemic group of patients (Table 2). The embryos in the prepandemic group were created from June 2019 to December 2019. The embryos in the pandemic group were created between June 2020 and December 2020.

### DISCUSSION

The COVID-19 pandemic has been responsible for radical changes in the delivery of fertility treatment globally. Smith et al.<sup>4</sup> developed a model to calculate the effects of shutting down fertility treatment and concluded that the discontinuation of fertility treatment for even '1 month could result in 269 fewer women having a live birth, due to increasing patient's age.' They postulated that more IVF cycles would be required to overcome infertility. In Italy, Setti et al.<sup>5</sup> demonstrated no differences in clinical pregnancy rates or spontaneous miscarriage rates before and during the pandemic. In total, 1749 fresh cycles (883 non-COVID-19 risk and 866 COVID-19 risk) and 1166 embryos and 63 oocytes warming cycles (538 and 37 during non-COVID and 628 and 26 during COVID-19 risk, respectively) were analysed. Clinical pregnancies per cycle

were not different: 370 (25.38%) in non-COVID versus 415 (27.30%) during COVID-19 risk.

### Limitations

Our sample size is small and not representative of the general population or other clinics. Our study is also more prone to selection bias. As mentioned, all IVF cycles were freeze-all, so we cannot comment on the pregnancy rates for IVF. We did not record sperm collection sites. We also did not collect patient and staff perceptions on the effects the different protocols could have.

### CONCLUSION

Treatment protocol adjustments due to COVID-19 did not adversely affect IUI, IVF, or FET outcomes at ONE Fertility. We can conclude that IUI and FET pregnancy rates at ONE Fertility were similar prepandemic and during the pandemic given fewer clinic visits, ultrasounds, and bloodwork. Interestingly, fertilization rate was better, and the number of cleaved embryos was higher in patients who had IVF treatment during the pandemic. It is reassuring to know the pandemic protocol adjustments did not have a negative impact on infertility treatment outcomes in our clinic, and this allows us to potentially keep these protocols in place.

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