First Trimester Pregnancy Outcomes in a Large ART Center From the Lombardy County (Italy) During the Peak COVID-19 Pandemic.

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Abstract

This study evaluates if the pandemic has influenced ART outcome in an asymptomatic infertile population treated at one of the major COVID-19 epicenters during the weeks immediately preceding the lockdown. All ART procedures during two time periods were used for comparison: November 1st, 2018 to February 28th, 2019 (non COVID-19 risk) and November 1st, 2019 to February 29th, 2020 (COVID-19 risk). We analyzed 1,749 fresh cycles (883 non COVID-19 risk and 866 COVID- 19 risk), 1,166 embryo and 63 oocytes warming cycles (538 and 37 during non COVID and 628 and 26 during COVID-19 risk respectively).

Clinical pregnancies per cycle were not different: 370 (25,38%) in non COVID vs 415 (27,30%) (p=0.237) during COVID-19 risk. There were no differences in biochemical pregnancy rates 52 (3,57%) vs 38 (2,50%) (p=0.089) nor in ectopic pregnancies 4 (1,08%) vs 3 (0,72%) (p=0,594), spontaneous abortions 84 (22,70%) vs 103 (24,82%) p=0,487, intrauterine ongoing pregnancies 282 (76,22%) vs 309 (74,46%) p=0.569. A multivariate analysis investigating differences in abortion rate showed no differences between the two times frame. Our results support no differences in asymptomatic infertile couples' ART outcomes between pre COVID and COVID-19 period in one of early and most severe pandemic area.

Introduction

At the beginning of 2020 the Italian Lombardy region was hit by an “epidemic tsunami” with almost no similar incidences in other parts of the World before [1]. Based on the first investigation on SARS-CoV-2 seroprevalence in one of the two initial lockdown areas in Lombardy, Lodi, at the beginning of the outbreak, the virus exposure was detected in 28% of asymptomatic blood donors [2]. The Lombardy region is home to 10 million inhabitants and accounts for 37% of cases and 53% of deaths of the country, as of April 15, 2020 [2], but the presented prevalence is likely to be underestimated by up to seven to ten times due to the lack of supplying of nasopharyngeal swabs during the pick period.Although officially the first coronavirus disease (COVID-19) case was reported on February 21st at the Codogno (Lodi) Hospital located 57 km (about 35 miles) from our Fertility Center, a recent epidemiological analysis demonstrated that the new severe acute respiratory syndrome virus 2 (SARS-CoV-2) was present in the Northern Italy at least 3 months (end of December 2019) before the official recognition [3]. Therefore, it is highly plausible that during the months of January-February 2020, before the interruption of clinical services and the lockdown, several infertile patients, unrecognized because asymptomatic for COVID-19 signs, were treated with ART cycles and achieved pregnancies. Available data, albeit very limited, on the impact of the SARS-CoV-2 on second and third trimester pregnancies suggest an increased risk for preterm deliveries [4,5] and the risk for vertical transmission is minimal, although a possible significant higher stillbirth rate has been recently suggested [6].

Case series have reported the detection of SARS-CoV-2 in different biological material, from semen to human breastmilk [7–10], and the possible vertical transmission of the virus from an infected mother to her new born [11] raised serious concerns in the embryologist community worldwide [12–14]. However, there is very limited information about the possible consequences of SARS-CoV-2 infection on ART performance and early pregnancy outcome.

The aim of this work is to fill the gap by evaluating early pregnancy outcomes after assisted reproduction during the early peak time of COVID-19 in Lombardy before the region officially ordered stopping all IVF treatments (with the exclusion of fertility preservation for oncologic patients and emergency or urgent procedures) and other treatments considered non-essential. Although the patients reported in this analysis were not positively identified as affected by COVID 19, the fact that they were treated during the unrecognized early peak of the pandemic make them a plausible exposed group and an interesting specific patient population to assess the effect, if any, of the pandemic on early stages of pregnancy, and on the biochemical and first trimester abortion rates [15].

Material And Methods

This is a retrospective observational analysis from a single, tertiary care, university-affiliated fertility centre, located in Lombardy, Rozzano, Milan, Italy, including all couples who underwent Assisted Reproduction (ART) procedures (fresh and frozen transfer cycles) during two time periods used for comparison: November 1st, 2018 to February 28th, 2019 (non COVID-19 risk) and November 1st, 2019 to February 29th, 2020 (COVID-19 risk.

No exclusion criteria were considered.

Patients were from all over Italy with a prevalence (70%) from the Lombardy region. The great majority of patients spent the entire period of the ovarian stimulation/monitoring in preparation for their treatments at 1-2 hours car distance from the hospital.

Information collected included: female age, BMI and smoking habits, duration of infertility, basal Follicle Stimulating Hormone (FSH), Anti Mullerian Hormone (AMH), Antral Follicular Count (AFC), indication for ART treatment, primary or secondary infertility and previous abortions. In addition, follow up data about pregnancy, first trimester abortion, and ectopic pregnancy outcome were collected until June 15, 2020.

No data about serological or oropharyngeal swab was considered. Of note, one embryologist with very mild symptoms had a confirmed positive oropharyngeal swab for SARS-CoV-2 during the study period, but no one else among medical, embryological, nurse and staff (about 60 people) had symptoms relatable to the viral infection.

Patient follow up included first Beta-hCG's performed 12 days after blastocyst transfer or 14 days after cleavage stage transfer and for pregnant patients repeated every 48 hours, until reaching at least 1,500 UI/ml. Transvaginal ultrasound was scheduled 4 weeks after transfer or earlier in case of abdominal pain and vaginal bleeding or abnormal rising Beta hCG levels. All non-essential ART activities were interrupted on April 16, 2020. Only emergency services, including fertility preservation for oncological patients and pregnancy follow-ups were allowed during the lockdown period.

Patients were required to email the results of ultrasounds if performed in other facilities. Every day, medical staff and assistants on duty called patients and updated the pregnancy outcome in their medical charts. Less than 5% of patients were lost at the follow-up that was considered concluded only when all known pregnant patients completed at least the 12th gestational week (as of June 15, 2020).

Statistical Analysis and variable description

Clinical pregnancy was defined as a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or or definitive clinical signs of pregnancy [16]. It therefore included ectopic pregnancy. Pregnancies with bHCG levels reaching less than 1,000 mIU/ml, and after exclusion of ectopic localization, were considered biochemical.

Data were described as number and percentage, or mean and standard deviation, as appropriated. Associations with period (pre and during COVID) were explored with $\chi 2$ test for categorical variables, or t student test for Gaussian continuous variables, or Mann Whitney for asymmetrical continuous variables. Association with abortion rate was explored with logistic regression analysis. Independent variable with a p value under 0.2 were then submitted to a multivariable logistic regression analysis. Pre and during COVID period variables were included in the multivariable analysis being the primary endpoint of the research. A p value under 0.05 was considered as significant. All analyses were conducted using Stata Statistical Software: Release15 (College Station, TX: StataCorp LLC).

Ethical approval

Generally, all patients undergoing ART procedures consent in writing that their medical records can be used for research purposes if anonymity and confidentiality is protected. Since both conditions were met, this study had expedited review and approval by the center's Institutional Review Board (IRB), Humanitas Clinical Institute Ethic Committee.

All methods were performed in accordance with the relevant guidelines and regulations and the present research has been performed in accordance with the Declaration of Helsinki.

An informed specific consent was obtained from all participants and/or their legal guardians.

The study was also approved by our Independent Ethical Committee on May 14th, 2020 (protocol n. 37/20).

Results

A total of 2,978 cycles were analyzed, 1,458 during non-COVID-19 risk (controls) and 1,520 during COVID--19 risk (exposure). Of these, 1,749 (58.7%) were fresh cycles, 883 in the period from November 1st, 2018 to February 28th, 2019 (Non COVID-19, controls) and 866 in the period November 1st, 2019 to February 29th, 2020 (COVID-19 risk exposure). There was a total of 1,166 (39.1%) embryo warming cycles, 538 during Non-COVID-19 and 628 during COVID-19 risk; finally, 63 (2.1%) oocytes warming cycles, 37 in the non COVID period and 26 during the COVID-19 risk were also assessed (see Table I).

Female age was 37.11 ± 4.17 in non COVID and 36.56 ± 4.19 in the COVID-19 period (p=0.026). No differences were found in other patient's demographic, ovarian response, and laboratory parameters (see table I). The number of transfers per cycle started (567 - 64.21% vs 496 - 57.27% p=0.003), number of embryos transferred (1.72 ± 0.51 vs 1.64 ± 0.5 p= 0.010), and the freeze all cycles (224 (27.32%) vs 257 (32.82%) P=0.016) were the only variables significantly different between the 2 periods (table I).

Cycle outcomes are described in Table II. In fresh cycles, implantation rates (24.02 ± 38.95 vs 28.39 ± 39.54 (p= 0.079), biochemical pregnancies (26 (2.94%) vs 13 (1.50%) p= 0.041, clinical pregnancies per cycle (189 (21.40%) vs 188 (21.71%) p=0.877 and per transfer (189 (33.33%) vs 188 (37.90%) p=0.120, ectopic pregnancies (3 (1.59%) vs 3 (1.60%) p=1.000, spontaneous abortions (37 (19.58%) vs 50 (26.60%) p=0.106, intrauterine ongoing pregnancies (149 (78.84%) vs 135 (71.81%) p=0.114) were not significantly different between the 2 periods analyzed (Table II). In warming embryo cycles the number of survived embryos (1.05 ± 0.22 vs 1.04 ± 0.25 p=0.430 and the mean number of embryos transferred (1.05± 0.22 vs 1.04 ± 0.23 p=0.285) were also not different (table II).

The total number of transfers were 2,061 (69.21%), 1044 in the Non COVID (71.60%) and 1017 (66.1%) during the COVID-19 risk (p=0.005). Pregnancies per cycle started were 370 (25.38%) vs 415 (27.30%) (p=0.237); pregnancies in fresh cycles 189 (21.40%) vs 188 (21.68%) (p=0.887); pregnancies in frozen embryos were 174 (32.34%) vs 222 (35.35%) (p=0.280). Pregnancies in frozen oocytes cycles were 7 (18,92%) vs 5 (19,23%) (p=0.975) in the two times frame, respectively. The overall implantation rate in percentage was 30.28 ± 43.59 vs 35.92 ± 45.93 (p=0.006), but it was not significantly different between fresh and frozen cycles. In fresh cycles it was 24.02 ± 38.95 vs 28.39 ± 39.54 p=0.079 while in frozen embryo transfer cycles it was 38.95 ± 49.89 vs 44.22 ± 50.71 (p=0.100) between the Non COVID and COVID-19 risk, respectively. The use of frozen oocytes cycles had an implantation rate of 18.97 ± 36.39 vs 13.16 ± 22.62 p=0.911 between the controls and exposure. Biochemical pregnancies 52 (3.57%) vs 38 (2.50%) (p=0.089), clinical pregnancies per cycle 370 (25.38%) vs 415 (27%) (p=0.237), ectopic pregnancies 4 (1.08%) vs 3 (0.72%) (p=0.594), spontaneous abortions 84 (22.70%) vs 103 (24.82%) (p=0.487), intrauterine ongoing pregnancies 282 (76.22%) vs 309 (74.46%) (p=0.569)(see Table III).

A multivariate analysis investigating differences in the abortion rate (Table IV) in the COVID and non-COVID-19 period showed no differences. There were 103 vs 312 spontaneous miscarriages, without a difference between the two times frame analyzed at the univariate analysis (p=0.487, OR 1.12 (0.81 - 1.56) and at the final multivariate model (p=0.953 OR 0.99 (0.68 - 1.44). The only variables significantly related to a higher abortion rate were female age (1.11 (1.06 - 1.17) p= <0.001), secondary infertility (0.57 (0.37 - 0.89), p=0.014), previous abortions (9.50 (6.09 - 14.81) p= <0.001), unexplained infertility (0.42 (0.23 - 0.76), p=0.004).

Discussion

The World Health Organization on 11th March 2020 declared the pandemic status for COVID-19, but Italy, mostly in the northern region of Lombardy, had already begun experiencing the severity of the COVID-19 since February 21, 2020, or even before. To prevent the diffusion of contagion, to avoid overwhelming the healthcare system, as well as reduce the worries of establishing a pregnancy during uncertain times, on March 17, 2020 the Superior Institute of Health (ISS) and the National Center of Transplant (CNT) issued prevention measures for the transmission of new Coronavirus infection (SARS-CoV-2) by ordering interruption of all non-essential medical services, including ART-related procedures. [17]. In view of the unknown effects of SARS-CoV-2 on mothers and fetuses, other international human reproduction societies published guidelines for managing patients who were already in cycle or planning to start ART treatments. On March 19, 2020, the European Society for Human Reproduction and Embryology (ESHRE) established to defer new pregnancies from embryo transfers and to reduce additional non-urgent hospitalizations of patients under fertility treatments in order to lighten the healthcare workload. After six days a 'COVID-19 working group' met in order to publish new ART guidelines after reviewing the latest scientific reports [14] . On March 17, 2020, the document named "Patient Management and Clinical Recommendations During the Coronavirus (COVID-19) Pandemic" published by ASRM recommended:

1. Suspend new ART cycles, including ovulation induction, intrauterine inseminations (IUIs), in vitro fertilization (IVF) and non-urgent gamete cryopreservation.
2. Suspend all embryo transfers.
3. Provide assistance and care for patients currently "in-cycle" or who need urgent stimulation and cryopreservation.
4. Suspend non-urgent surgeries and diagnostic procedures.
5. Avoid in-person interactions. Other updating followed [4] over the weeks.

These national and international guidelines were issued to safeguard the health of ART operators, of couples undergoing ART and newborns, during the COVID-19 pandemic [18].

There is still a paucity of information about the impact, if any, of COVID 19 infection on early pregnancy (first trimester) outcome. Since it is very plausible that the novel SARS-COV2 virus could have spread, unrecognized, in Lombardy area already few months before ART treatments were suspended, this study investigated whether the several infertile asymptomatic patients who were treated and achieved pregnancies during that at risk time-period had a different pregnancy outcome when compared to a similar infertile population dataset taken from the same season but one year before (non-COVID-19 risk).

The results of our analysis showed no differences in early pregnancy outcomes between the controls and the COVID-19 risk exposure in terms of implantation, pregnancy, biochemical and abortion rate both in fresh and frozen ART cycles. The lack of an increased risk for miscarriage or other adverse outcome in early pregnancies obtained during high risk COVID-19 exposure is reassuring.

The strength of the present study relays on the large sample analyzed in a geographical area considered the epicenter of the pandemic in Europe and where the incidence of SARS-COV-2 positive cases was very high in general asymptomatic population.

SARS and MERS epidemics showed no correlation with fetal malformations. However, the clinical course of COVID-19 disease and the response to treatments seem to differ from other previous types of coronaviruses [19]. In order to fully understand pathogenesis and epidemiology of SARS-CoV-2 during pregnancy, further research is needed focusing on the time of maternal infection, gestational age, role of comorbidity factors, and adverse outcomes. Luckily, preliminary studies on pregnant women infected with SARS-CoV-2 give an optimistic outlook regarding the clinical course [20].

During the first months of the pandemic, the American Society for Reproductive Medicine Coronavirus/COVID-19 Task Force reviewed ninety-seven articles about pregnancy and coronavirus in order to clarify the effect of the novel virus on human reproduction and pregnancy [8]. At the time, no reported studies did examine pregnant COVID-19 patients at earlier stages of pregnancy. Few data regarding the effect of SARS–CoV-2 on human reproduction are available because the virus is novel and has only recently infected humans. The SARS–CoV-2 virus enter into human cells using ACE2 receptors. The reproductive system in men expresses ACE2 in Leydig cells in the testis and it may play a role in spermatogenesis. Gonadotropin-dependent expression of ACE2 has been reported also in human female gonads [21,22], but it is still unknown if the SARS–CoV-2 virus uses ACE2 receptors in the human reproductive system and what, if any, impact this might have on oocyte quality, embryo development, or the consequent pregnancy. Our data is an indirect confirmation (since we did not show presence or absence of the virus in our asymptomatic pregnant ART patient population) of existing evidence from two case-control studies (involving 46 patients and 287 controls) showing that COVID-19 during early pregnancy is not more severe than among non-pregnant women [23,24].

The real impact that COVID-19 infection can cause on fertility and human reproduction remain obscure. Despite the overwhelming magnitude of the disease and its worldwide prevalence, information regarding the effects of the novel coronavirus on human reproduction are currently limited. This lack of evidence should not be considered reassuring because less than 1 year have elapsed since the novel coronavirus jumped species and infected humans.

It is important to study other possible long-term effects on male and female gametes , specifically whether there might be shedding of virus in some individuals that might even affect the safety and storage of gametes [18]. Evidence continues to emerge regarding effects of the novel coronavirus in pregnancy and some initial reports suggest that complications, particularly after delivery, may be increased [9], even if outcomes for infants are largely reassuring when considering potential effects of SARS-CoV-2 infection acquired before or during birth [5,25]. Further studies are necessary, and additional data regarding outcomes of early pregnancies in demonstrated infected pregnant women should be collected [26].

The main limitation of this study is the retrospective nature of the analysis and the high plausibility (but not corroborated) of the COVID-19 exposure since the ART treatments occurred during the early peak of the Italian pandemic.

Conclusion

Our preliminary dataset mitigated concerns for negative reproductive consequences from COVID-19 pandemic and demonstrated no increased risk for miscarriage during the first trimester of ART pregnancies achieved during the emergence of the COVID 19 health crisis.

Declarations

Authorship contribution

PELS, FC, VI and CR, designed the study, collected data, and drafted the manuscript. VC, AB and EA collected clinical data. EM analyzed clinical data and performed the statistical analysis. PP analyzed data and revised the manuscript. All authors participated to critical discussion and final manuscript.

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Conflict of interest

Authors have no conflict of interest to declare.

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Tables

Table I. Patients, demographics, indications for ART and cycle characteristics for the total fresh cycles analyzed in the non COVID and COVID-19 times frame.

Fresh Cycles	PRE COVID	COVID-19	p
N	883	866	
Female age	37.11 ± 4.17	36.56 ± 4.19	0.026
Years of infertility	3.8 ± 2.6	3.72 ± 2.45	0.734
BMI	22.26 ± 3.34	22.41 ± 3.37	0.299
Smoking	146 (16.53%)	177 (20.44%)	0.035
Secondary infertility	312 (35.33%)	272 (31.41%)	0.082
Previous deliveries	41 (4.64%)	28 (3.23%)	0.130
Previous abortions	275 (31.14%)	234 (27.02%)	0.058
Basal FSH	8.55 ± 3.61	8.67 ± 3.59	0.313
AMH	2.46 ± 2.49	2.5 ± 2.65	0.702
Antral follicular count	11.24 ± 8.11	11.72 ± 8.51	0.396
Indication to treatment			
Male	227 (25.71%)	239 (27.60%)	0.371
Tubal	55 (6.23%)	36 (4.16%)	0.051
Unexplained	103 (11.66%)	86 (9.93%)	0.243
Male and female factor	214 (24.24%)	207 (23.90%)	0.871
Ovulatory	11 (1.25%)	11 (1.27%)	0.963
Reduced ovarian reserve	183 (20.72%)	138 (15.94%)	0.010
Multiple female factors	49 (5.55%)	35 (4.04%)	0.140
Other	14 (1.59%)	8 (0.92%)	0.214
Stimulation protocol			0.320
Antagonist cycle	692 (78.37%)	665 (76.79%)	
Agonist long short	46 (5.21%)	60 (6.93%)	
Agonist flare	145 (16.42%)	141 (16.28%)	
Total sperm count (x 10^6)	74.07 ± 90.82	71.85 ± 76.31	0.393
Progressive motility %	23.59 ± 9.87	24.6 ± 11.56	0.221
Oocyte retrievals	820	783	0.064

Fresh Cycles	PRE COVID	COVID-19	p
Cycles Cancelled	63 (7.13%)	83 (9.58%)	0.064
Mean Oocytes retrieved	9.32 ± 6.06	10.05 ± 6.64	0.070
No oocytes retrieved or not usable	18 (2.04%)	14 (1.62%)	0.510
Mature Oocytes	6.98 ± 4.93	7.35 ± 5.29	0.376
Fertilization rate %	76.66 ± 23.56	74.52 ± 24.75	0.113
Cleavage rate %	98.63 ± 7.64	98.86 ± 5.22	0.879
Transfers/cycle	567 (64.21%)	496 (57.27%)	0.003
Mean Embryos transferred	1.72 ± 0.51	1.64 ± 0.5	0.010
Cleavage stage	473 (83.42%)	404 (81.45%)	
Blastocyst stage	94 (16.58%)	92 (18.55%)	
Frozen embryos	2.39 ± 1.46	2.59 ± 1.62	0.097
Frozen Oocytes	8.19 ± 4.08	8.3 ± 4.01	0.887
Freeze All Cycles	224 (27.32%)	257 (32.82%)	0.016

Table II. ART cycles outcomes in fresh, warmed embryos and warmed oocytes in the pre COVID and COVID-19 times frame.

	PRE COVID	COVID	p
	FRESH ET		
N.	883	866	
Female age	37.11 ± 4.17	36.56 ± 4.19	0.026
embryo transferred	1.72 ± 0.51	1.64 ± 0.5	0.010
Cleavage stage	473 (83.42%)	404 (81.45%)	0
Blastocyst stage	94 (16,58%)	92 (18,55%)	0.399
Implantation rate %	24.02 ± 38.95	28.39 ± 39.54	0.079
Biochemical Pregnancies	26 (2.94%)	13 (1.50%)	0.041
Clinical Pregnancies per cycle	189 (21.40%)	188 (21.71%)	0.877
Clinical Pregnancies per transfer	189 (33.33%)	188 (37.90%)	0.120
Ectopic Pregnancies	3 (1.59%)	3 (1.60%)	1.000
Spontaneous abortions	37 (19.58%)	50 (26.60%)	0.106
Intrauterine ongoing pregnancies	149 (78.84%)	135 (71.81%)	0.114
Single pregnancies	127 (85.23%)	112 (82.96%)	0.601
Twin pregnancies	22 (14.77%)	23 (17.04%)	
	EMBRYO WARMINGS		
N.	538	628	
Female age at freezing	29.6 ± 13.8	28.9 ± 14.7	0.782
warmed embryos	1.058 ± 0.23	1.053 ± 0.24	0.565
survived embryos	1.051 ± 0.22	1.043 ± 0.25	0.430
embryo transferred	1.049 ± 0.22	1.036 ± 0.23	0.285
Cleavage stage	32 (7.14%)	23 (4,58%)	0.091
Blastocyst stage	409 (91.29%)	464 (92,43%)	
Embryos from other institutions	7 (1.56%)	15 (2,99%)	0.195
Implantation rate %	38.95 ± 49.89	44.22 ± 50.71	0.100
Biochemical Pregnancies	25 (4.65%)	23 (3,66%)	0.399
Clinical Pregnancies per cycle	174 (32.34%)	222 (35.35%)	0.280
Clinical Pregnancies per transfer	174 (38.84%)	222 (44.22%)	0.093

	PRE COVID	COVID	p
Ectopic Pregnancies	1 (0.57%)	0 (0.00%)	0.439
Spontaneous abortions	45 (25.86%)	53 (23.87%)	0.649
Intrauterine ongoing pregnancies	128 (73.56%)	169 (76.13%)	0.559
Single pregnancies	127 (99.22)	164 (97.04%)	0.187
Twin pregnancies	1 (0.78%)	5 (2.96%)	
	OOCYTE WARMINGS		
N.	37	26	
Female age at freezing	30.2 ± 12.4	25.9 ± 15.0	0.159
warmed oocytes	6.66 ± 2.62	6.9 ± 2.34	0.629
survived oocytes	4.94 ± 2.54	5.85 ± 1.84	0.156
fertilized oocytes	4 ± 2.48	4.5 ± 1.76	0.482
transferred embryos	1.68 ± 0.6	1.75 ± 0.55	0.639
Cleavage stage	29 (100.00%)	18 (94.74%)	0.396
Blastocyst stage	0 (0.00%)	1 (5.26%)	
Pregnancies	7	5	
Implantation rate %	18.97 ± 36.39	13.16 ± 22.62	0.911
Biochemical Pregnancies	1 (2.70%)	2 (7.69%)	0.564
Clinical Pregnancies per cycle	7 (18.92%)	5 (19.23%)	0.975
Clinical Pregnancies per transfer	7 (24.14%)	5 (26.32%)	0.865
Ectopic Pregnancies	0	0	
Spontaneous abortions	2 (28.57%)	0 (0.00%)	0.470
Intrauterine ongoing pregnancies	5 (71.43%)	5 (100%)	0.470
Single pregnancies	3 (60.00%)	5 (100%)	0.444
Twin pregnancies	2 (40.00%)	0	

Table III. Summary ART cycles outcome in the total population during pre COVID and COVID-19 times frame.

Variable	PRE COVID	COVID-19	p
Total cycles (n)	1458	1520	
Fresh Cycles	883 (57.13%)	866 (56.94%)	
Frozen Embryos	538 (26.90%)	628 (41.29%)	
Frozen Oocytes	37 (2.54%)	26 (1.71%)	
Total transfers (n)	1044 (71.60%)	1017 (66.91%)	0.005
Pregnancies (% per cycle)	370 (25.38%)	415 (27.30%)	0.237
Pregnancies fresh cycles (% per cycle)	189 (21.40%)	188 (21.68%)	0.887
Pregnancies frozen embryos (% per cycle)	174 (32.34%)	222 (35.35%)	0.280
Pregnancies frozen oocytes (% per cycle)	7 (18.92%)	5 (19.23%)	0.975
Implantation rate	30.28 ± 43.59	35.92 ± 45.93	0.006
Implantation rate fresh cycles	24.02 ± 38.95	28.39 ± 39.54	0.079
Implantation rate frozen embryos	38.95 ± 49.89	44.22 ± 50.71	0.100
Implantation rate frozen oocytes	18.97 ± 36.39	13.16 ± 22.62	0.911
Biochemical Pregnancies	52 (3.57%)	38 (2.50%)	0.089
Clinical Pregnancies (% per cycle)	370 (25.38%)	415 (27,30%)	0.237
Ectopic Pregnancies	4 (1.08%)	3 (0.72%)	0.594
Spontaneous abortions	84 (22.70%)	103 (24.82%)	0.487
Intrauterine ongoing pregnancies	282 (76.22%)	309 (74.46%)	0.569
Single pregnancies	257 (91.13%)	281 (90.94%)	0.934
Twin pregnancies	25 (8.87%)	28 (9.06%)	

Table IV. Univariate and multivariate analysis for variables potentially related to abortion rate in the analyzed population.

				univariate		multivariate final model	
	Abortion	Not Abortion	p	OR	p	OR	p
N	187	598					
COVID- non COVID-19 risk	103 (55.08%)	312 (52.17%)	0.487	1.12 (0.81 - 1.56)	0.487	0.99 (0.68 - 1.44)	0.953
Female age	37.30 ± 4.18	35.53 ± 3.86	<0.001	1.12 (1.08 - 1.19)	<0.001	1.11 (1.06 - 1.17)	<0.001
Years of infertility	4.28 ± 2.74	3.97 ± 2.53	0.3602	1.04 (0.98 - 1.11)	0.164		
BMI	21.85 ± 3.00	21.93 ± 3.07	0.9191	0.99 (0.94 - 1.04)	0.748		
Smoking	43 (22.99%)	122 (20.40%)	0.447	1.17 (0.79 - 1.73)	0.448		
Secondary infertility	91 (48.66%)	200 (33.44%)	<0.001	1.89 (1.35 - 2.63)	<0.001	0.57 (0.37 - 0.89)	0.014
Previous deliveries	13 (6.95%)	33 (5.52%)	0.466	1.28 (0.66 - 2.48)	0.467		
Previous abortions	131 (70.05%)	144 (24.08%)	<0.001	7.38 (5.12 - 10.62)	<0.001	9.50 (6.09 - 14.81)	<0.001
Basal FSH	7.93 ± 2.72	8.06 ± 3.94	0.7155	0.99 (0.94 - 1.04)	0.679		
AMH	2.95 ± 2.56	3.16 ± 2.94	0.2795	0.97 (0.91 - 1.03)	0.377		
Antral follicular count	13.13 ± 10.42	14.12 ± 9.32	0.0439	0.99 (0.97 - 1.01)	0.325		
Indication to treatment							
Male	65 (34.76%)	233 (38.96%)	0.301	0.83 (0.59 - 1.18)	0.302		
Tubal	9 (4.81%)	36 (6.02%)	0.535	0.79 (0.37 - 1.67)	0.536		
Unexplained	18 (9.63%)	81 (13.55%)	0.159	0.68 (0.40 - 1.17)	0.161	0.42 (0.23 - 0.76)	0.004
Male and female factor	38 (20.32%)	118 (19.73%)	0.860	1.04 (0.69 - 1.56)	0.860		
Ovulatory	4 (2.14%)	6 (1.00%)	0.227	2.16 (0.60 - 7.73)	0.238		

Reduced ovarian reserve	15 (8.02%)	54 (9.03%)	0.671	0.88 (0.48 - 1.60)	0.671
Multiple female factors	11 (5.88%)	19 (3.18%)	0.092	1.90 (0.89 - 4.08)	0.097
Other	0	4 (0.67%)	0.262	NC	
Embryos transferred	1.37 ± 0.52	1.36 ± 0.48	0.9105	1.06 (0.76 - 1.49)	0.718
Procedure (fresh)	87 (46.52%)	290 (48.49%)	0.638	0.92 (0.66 - 1.28)	0.638