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The SARS-CoV-2 psychological impact on assisted reproductive treatments delay and time to pregnancy

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ABSTRACT

Objective. Couples undergoing fertility treatment procedures are prone to developing feelings of psychological distress caused by their infertility diagnosis, and this emotional toll can be exacerbated by the invasiveness of the treatments for both partners, as well as external factors, such as the SARS-CoV-2 pandemic.

Materials and Methods. A questionnaire, composed of 6 sections for a total of 44 questions, was developed and applied to assess how couples were affected emotionally. More specifically it was used to analyse the differences between couples who decided to take a break from ART procedures lasting over 6 months after an initial failure and those that kept their therapeutic path after an initial failure. A section of the questionnaire was focused on the SARS-CoV-2 pandemic.

Results. The questionnaire was completed by 79 female subjects and 55 male subjects. The results of the aforementioned analysis showed that the pandemic per se did not have a significant impact in terms of treatment discontinuation. Conversely, relevant factors with a significant impact on treatment time frame were the concordance of couples' answers to the questionnaire on the distress associated with infertility, and marital distress ($p = 0.04$), evaluated through the same questionnaire.

Conclusions. The concordant perception of having a fertility problem from both partners and the stability of the relationship were shown to be the most relevant factors affecting treatment dropout. Moreover, the number of frozen embryos showed an inverse correlation. Of outmost importance, the SARS-CoV-2 pandemic showed no correlation with the ART delay of a second embryo transfer.

INTRODUCTION

The assisted reproductive techniques (ART) infertility path is a long, complex, and exhausting medical diagnostic and therapeutic option for infertile couples. However, despite the presence of adequate solutions, from Intra-Uterine Insemination (IUI) to *In Vitro* Fertilization (IVF) and Intra-Cytoplasmic Sperm Injection (ICSI), lots of efforts are still necessary to increase the overall live birth rates. Conversely, the patient expectations suffer from the recurrent unsuccess after embryo transfers and eventual miscarriages [1]. On this regard, in order to reach greater ART outcomes in terms of live birth, new perspectives considering both IVF centre protocols and social issues address the time to pregnancy as one of the leading success factors and a key clue for improving outcomes [2]. Often, a delay is seen on couples' treatments, especially when dealing with frozen thawed embryo transfers, which has a plethora of aetiologies such as stress, costs, change in couples' desire, change of partner or divorce, spontaneous pregnancy, and psychological conditions [3]. However, from 2020, a new important factor, the SARS-CoV-2 pandemic, has affected pregnancy outcomes [4, 5] and couples' delay on ART treatment [6]. Although the necessity to postpone treatments due to the pandemic has been considered of exceptional importance in early 2020, in the subsequent period the most important SARS CoV-2 fertility affection is linked to the psychological burden caused by the illnesses and the quarantine. According to this, we aim to investigate the connection between the SARS-CoV-2 pandemic and the postponement of ART treatments, considering the two in a pairwise approach. We present a single centre observational study regarding the impact of the SARS-CoV-2 pandemic on the postponement of ART treatments through the administration of a psychological questionnaire. Our main question can be summarised as: is the SARS-CoV-2 pandemic responsible for a delay in ART treatments?

MATERIALS AND METHODS

Study design

This is an observational retrospective study provided by our IVF centre on infertile couples undergoing ART treatments. We recruited all consecutive couples accessing our IVF centre at IRCCS San Raffaele Hospital and Vita-Salute San Raffaele

University (Milan, Italy). We recruited patients independently by age and infertility aetiology.

Inclusion criteria

The inclusion criteria were:

- Couples whose women underwent at least one ovarian pick-up between January 2020 and November 2021.
- Couples whose laboratory outcomes after ovarian pick-up provided an embryo number ≥ 2 and at least one frozen embryo.
- Couples who underwent a first embryo transfer attempt with negative beta-HCG serum results. This embryo transfer included both fresh or frozen thawed embryo transfers and was independent from the type of endometrial preparation (natural or artificial).

We divided the patients in two groups: group A included couples who underwent a second embryo transfer in 180 days; group B included couples who underwent a second embryo transfer after 180 days from the previous one. The 180 days cut-off was decided since we reasonably considered this time acceptable for couples for resolving eventual clinical problems affecting the second embryo transfer schedule for example the need of further investigations prior the subsequent ART step.

Exclusion criteria

The exclusion criteria were:

- Couples who underwent intrauterine insemination.
- Couples who made ovarian pick-up before the SARS-CoV-2 pandemic (January 2020).
- Couples who were unable to properly answer the questionnaire (provided in Italian) for language difficulties.

The questionnaire administration

Every patient involved in the study signed aprioristically an informed consent for the collection of data for scientific purposes (BC-GINEOS protocol) regarding their anamnesis, treatment outcomes, and follow-up information. Every consecutive couple received a first telephone interview in which the infertility specialist introduced the purpose of the study, explained the methods, and invited them to take part. Those couples who agreed to participate were sent an informed consent form and a link to a Google module for each partner. Since most of the phone calls were

made to the female partner, the infertility specialist emphasised the need for both partners to answer the questionnaire. The questionnaire sent to the couples is a modified version from Smith *et al.* [7], presented in **Appendix 1** with the modification we did according to the aim of our study. In particular, we used an Italian version. The questionnaire we used is composed by three sections divided as follows:

- Section 1: questions relating to marital status and the reasons for the interruption of the ART treatment;
- Section 2: questions relating to the impact of SARS-CoV-2, vaccination status and contracted infections;
- Section 3 [7]:
 - Group A - Personal SARS-CoV-2 impact: 5 questions;
 - Group B - Sexual SARS-CoV-2 impact 5 questions;
 - Group C - Marital status SARS-CoV-2 impact: 7 questions;
 - Group D - Social SARS-CoV-2 impact 20 questions.

Blinding and concordance analysis

All the answers were inserted into a database where every couple was coded with an alphanumeric code. The total score was calculated for every section of the questionnaire for every participant. In order to calculate the concordance between the two partners questionnaire answers, we divided the score in each question group in high, medium and low score. With this concordance analysis based on 55 couples, we then performed a descriptive analysis, and a model which could predict the time for couples continuing the ART path with the second embryo transfer.

Predictive model analysis

In order to create a model which could predict the second embryo transfer delay according to couples' characteristics, we performed a step-forward analysis on the couple characteristics and the questionnaire answers. Specifically, we inserted: the number of cryo-preserved embryos, and health issues. Subsequently, a similar analysis was performed on the 55 couples where both partners answered the questionnaire.

Statistical analysis

Statistical analysis was performed by using SPSS v.22.0 (IBM Corp., Armonk, NY, USA). Continuous

variables were reported as mean with standard deviation (SD), whereas qualitative variables were presented as absolute frequencies and percentages. Comparisons between categorical variables were tested by using contingency tables and chi-square test or Fisher's test when necessary. Comparisons between normally distributed continuous variables were made by using Student's t-test. A value of $p < 0.05$ was considered as statistically significant. We performed a Spearman correlation between questions and sections of the questionnaire.

RESULTS

We invited 95 couples answering our questionnaire; 91 of the partners reached were the female partner of the couples. A total of 134 patients answered the questionnaire from January 2022 and April 2022: 79 female partners and 55 male partners. Since the main outcomes of our study are related to the dyadic approach on ART, we performed the concordance statistical analysis only on 55 couples, which provided both the female and male questionnaire.

ART delay

During the first analysis, with the 180 days cut-off, we initially found that couples whose both partners answered the questionnaire had a different delay in ART path compared to the group where only the female answered the questionnaire. In particular, the proportion of couples whose both partners answered the questionnaire and performed a second embryo transfer in the next 180 days after the first attempt was 75% and was slightly lower at 61% if they performed the second embryo transfer after 180 days. This pattern showed a different trend for the only-female-questionnaire-answer group.

Questions and sections correlation

We performed a Spearman correlation between questions and sections of the questionnaire (**Figure 1**). As expected, the questions comprised in the same sections presented a positive correlation. At the same time, sections regarding the personal (GROUP A), sexual (GROUP B), and social impact (GROUP D) showed a positive correlation between them. Interestingly, the marital status (GROUP C) impact presented a different correlation with the other sections. Deepening the aspect of single ques-

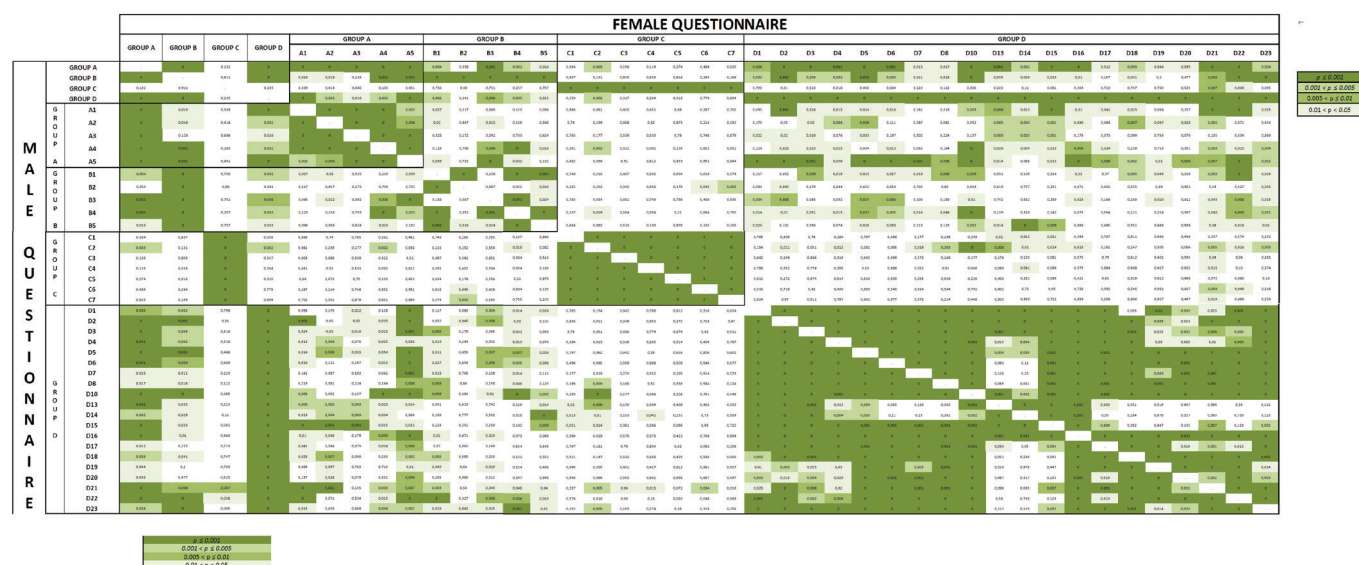


Figure 1. Mean ART delay according to the presence of one couples' partner SARS-CoV-2 infected.

tions which in the same section showed a different correlation trend, we found the following results:

- Group A - Personal impact: questions in this section were positively correlated between them and with sexual and social sections. They showed no correlation with the marital status impact section.
- Group B - Sexual impact: questions in this section showed a similar trend as above with intra-section questions and the personal and social impact sections. The only exception regarded the question B2 "I feel just as attractive to my partner as before our fertility problem" which showed a lack of correlation with all other questions.
- Group C - Marital status impact: this section showed the lowest correlation with all other sections. However, the question C2 "What effect have your fertility problems had on how often you and your partner have disagreements and arguments?" showed a positive correlation with one question of the personal impact section, with one question of the sexual impact section, and with 12 questions of the social impact section.
- Group D - Social impact section: questions in this section showed a similar trend as above with intra-section questions and the personal and sexual impact sections. A lack of correlation with the marital status impact sections was confirmed with the exception of the question D21 "How often do you feel that you don't have anything in common with your friends who have not had fertility problems?" which was positively correlated with 5 questions of the marital status impact section.

What are the main causes of ART delay? And what is the SARS-CoV-2 impact?

When addressing the group of reasons which hampered the second embryo transfer delay, data showed a major impact related to the health reasons group, which was responsible for a median transfer delay of 109.3 days (**Table 1**). The couples included in the external reasons group showed a median transfer delay of 82.53 days, and the SARS-CoV-2 reasons group showed a median transfer delay of 26.967 days. Interestingly, we deepened our analysis addressing the scores of the two questions in section 2: "How much is the influence of SARS-CoV-2 on your marital life?" and "How much is the influence of SARS-CoV-2 on your ART path"? A negative trend correlation was found with the scores of question A trend in the embryo transfer delay and a slight positive trend in question B. However, results were not statistically significant (**Table 2**).

Moreover, we analysed the proportion of patients vaccinated and the subsequent eventual infection. 25 female questionnaires presented at least one of the partner which encountered the SARS-CoV-2 infection, and 54 female questionnaire presented couples without SARS-CoV-2 infection. Considering the SARS-CoV-2 infection of one partner (independently male or female) and the conversely quarantine of the second, we investigated the second embryo transfer delay. Accordingly, the mean transfer delay in the SARS-CoV-2 infection couples was 16 days, but with not statistically significance (data not shown).

Table 1. Reasons group accounting for embryo transfer delay, specifically: health reasons group, external reasons group, SARS-CoV-2 group.

	Unstandardized coefficients		Standardized coefficients	t	Sig.	95% Confidence Interval for B	
	B	Std. error	Beta			Lower bound	Upper bound
(Constant)	129.527	21.278		6.087	.000	87.140	171.914
1 External Reasons	82.530	37.402	.251	2.207	.030	8.022	157.039
Health Issues	109.315	37.100	.339	2.946	.004	35.408	183.222
COVID Impact	26.967	62.014	.048	.435	.665	-96.571	150.505

Table 2. Correlation between ART delay and scores of two questions: A) "How much is the influence of SARS- CoV-2 on your marital life?" and B) "How much is the influence of SARS- CoV-2 on your ART path"?

	Unstandardized coefficients		Standardized coefficients	t	Sig.	95% Confidence Interval for B	
	B	Std. error	Beta			Lower bound	Upper bound
(Constant)	202.506	32.759		6.182	.000	137.262	267.751
1 A	-7.666	6.003	-.162	-1.277	.205	-19.621	4.289
b	.429	5.419	.010	.079	.937	-10.364	11.222

Are the partners concordant in their questionnaire answers?

Addressing the concordance between partner answers, we found that in the marital status (group C) SARS-CoV-2 impact session for the two following questions the 87% of couples answered concordantly: C1) "What effect have your fertility problems had on how much you enjoy the time you spend with your partner?" and C2) "What effect have your fertility problems had on how often you and your partner have disagreements and arguments?".

Moreover, in the personal (group A) SARS-CoV-2 impact session a different concordance was seen for the two following questions: A4) "Because of your fertility problems, how often have you felt that you must have done something to deserve these problems?" and A5) "Because of your fertility problems, how often have you felt defective?". In particular, the concordance intra-couple was 36%, since women showed a greater importance given to the infertility diagnosis on this topic (data not shown).

What is the time delay related to the couples' questionnaire concordance?

The next step of our analysis relied in analysing the second embryo transfer delay according to couples' questionnaire concordance on every section. Interestingly but not surprisingly, the only one section which showed a statistically significant correlation was the marital status section. On this regard, the

presence of partner concordance on the marital status question was related with a delay of 75 days on the second embryo transfer (data not shown).

Can we predict the ART delay according to couple characteristics and the questionnaire answers?

First, regarding the model according only to women answers, we found the following correlation (**Table 3**):

- For every new frozen embryo, the second embryo transfer delay decreased of 16 days.
- Health issues: for every woman accusing health issues for the ART delay, the second embryo transfer delay increased of 83 days.
- For the question D13 "How often do you feel that your partner doesn't understand your feelings about having a (another) baby?" we noticed a decrease of 9 days for the second embryo transfer delay for every point.
- For the question D18 "How often do you feel that your friends don't understand what trying to have a (another) baby is like for you?" we noticed an increase of 13 days for the second embryo transfer delay for every point.
- For the question D20 "How often do you feel that people avoid talking to you about your problems having a (another) baby?" we noticed a decrease of 9 days for the second embryo transfer delay for every point.

Secondly, analysing this predictive model for the 55 couples with both partner participation on the questionnaire, we found the following results (**Table 4**):

Table 3. Predictive model of ART delay according to female answers to the questionnaire.

	Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. error	Beta			Lower bound	Upper bound
1	(Constant)	241.584	28.151		8.582	.000	185.516	297.652
	Frozen thawed embryo	-18.522	6.432	-.314	-2.880	.005	-31.334	-5.711
2	(Constant)	227.596	28.188		8.074	.000	171.443	283.749
	Frozen thawed embryo	-19.381	6.287	-.328	-3.083	.003	-31.906	-6.856
	Health issues	74.538	33.830	.235	2.203	.031	7.145	141.931
3	(Constant)	240.221	28.772		8.349	.000	182.892	297.550
	Frozen thawed embryo	-17.316	6.321	-.293	-2.740	.008	-29.910	-4.722
	Health issues	76.622	33.416	.241	2.293	.025	10.040	143.204
	D13	-7.128	4.134	-.184	-1.724	.089	-15.365	1.110
4	(Constant)	196.529	34.878		5.635	.000	127.017	266.040
	Frozen thawed embryo	-16.410	6.192	-.278	-2.650	.010	-28.750	-4.070
	Health issues	78.940	32.674	.248	2.416	.018	13.820	144.060
	D13	-8.878	4.124	-.230	-2.153	.035	-17.097	-.659
	D18	9.189	4.340	.222	2.117	.038	.539	17.838
5	(Constant)	212.817	35.085		6.066	.000	142.875	282.758
	Frozen thawed embryo	-16.025	6.067	-.271	-2.642	.010	-28.119	-3.932
	Health issues	83.054	32.062	.261	2.590	.012	19.140	146.968
	D13	-8.930	4.039	-.231	-2.211	.030	-16.980	-.879
	D18	13.266	4.701	.320	2.822	.006	3.895	22.637
	D20	-8.898	4.384	-.226	-2.030	.046	-17.637	-.159

- For every frozen embryo, the second embryo transfer delay decreased of 17 days.
- Marital status impact: for concordant couples' answers in this section, we registered a second embryo transfer delay of 108.5 days.
- For the question D20 "How often do you feel that people avoid talking to you about your problems having a (another) baby?" we noticed an increase of 81 days for the second embryo transfer delay for every point in case of concordance.
- For the question D19 "How often do feel that you can't talk to your friends about your problems having a (another) baby?" we noticed a decrease of 66.5 days for the second embryo transfer delay for every point in case of concordance.
- For the question C7 "What effect have your fertility problems had on how close you feel to your partner?" we noticed a decrease of 92.3 days for the second embryo transfer delay for every point in case of concordance.

DISCUSSION

Our results can be addressed and discussed in two main areas of interest: the SARS-CoV-2 pan-

demic and the psychological impact of ART treatments in ART delay. During the early 2020, lots of doubts about the viral impact on pregnant women and emerged, forcing IVF centres in reducing their treatments (until the closing) and adopting the freeze all technique for every controlled ovarian stimulation ongoing [8]. Specifically, on March 17, 2020, the American Society for Reproductive Medicine (ASRM) published guidelines (ASRM 2020) [9], followed on March 19 by the European Society for Human Reproduction and Embryology (ESHRE 2020) [10], recommending the stop of all new controlled ovarian stimulation cycles, excluding urgent cryopreservation. In case of ongoing treatments, cycles could be continued with a recommendation of the freeze-all technique.

Subsequently, following guidelines suggestion and considering the psychological impact that both SARS-CoV-2 and the lack of IVF centre availability had in infertile couples, a global IVF re-opening occurred, according to local condition [11].

According to this, we aimed to assess the link between ART delay and SARS-CoV-2 impact, investigating deeply the psychological issues of infertile couples.

Table 4. Predictive model of ART delay according to both partners' answers to the questionnaire.

	Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. error	Beta			Lower bound	Upper bound
1	(Constant)	228.044	28.231		8.078	.000	171.420	284.669
	Frozen thawed embryo	-18.423	6.455	-.365	-2.854	.006	-31.370	-5.476
2	(Constant)	184.742	32.661		5.656	.000	119.204	250.281
	Frozen thawed embryo	-16.721	6.232	-.331	-2.683	.010	-29.227	-4.215
	GROUP C	70.272	29.642	.293	2.371	.021	10.791	129.753
3	(Constant)	148.419	35.185		4.218	.000	77.782	219.055
	Frozen thawed embryo	-16.368	5.995	-.324	-2.730	.009	-28.403	-4.333
	GROUP C	71.842	28.510	.299	2.520	.015	14.605	129.079
	D20	64.857	28.328	.270	2.289	.026	7.985	121.728
4	(Constant)	150.767	34.188		4.410	.000	82.098	219.435
	Frozen thawed embryo	-13.950	5.943	-.276	-2.347	.023	-25.887	-2.013
	GROUP C	86.120	28.574	.359	3.014	.004	28.726	143.513
	D20	86.946	29.603	.362	2.937	.005	27.486	146.406
	D19	-61.931	30.659	-.258	-2.020	.049	-123.511	-.352
5	(Constant)	219.236	45.738		4.793	.000	127.322	311.150
	Frozen thawed embryo	-15.129	5.762	-.300	-2.626	.012	-26.708	-3.550
	GROUP C	109.657	29.651	.457	3.698	.001	50.072	169.242
	D20	81.497	28.683	.339	2.841	.007	23.855	139.138
	D19	-67.521	29.704	-.282	-2.273	.027	-127.213	-7.830
	C7	-84.811	39.232	-.262	-2.162	.036	-163.651	-5.972
6	(Constant)	512.983	168.684		3.041	.004	173.822	852.144
	Frozen thawed embryo	-16.929	5.721	-.335	-2.959	.005	-28.432	-5.426
	GROUP C	108.505	28.996	.452	3.742	.000	50.204	166.806
	D20	81.141	28.044	.338	2.893	.006	24.754	137.527
	D19	-66.544	29.046	-.278	-2.291	.026	-124.945	-8.143
	C7	-92.349	38.583	-.285	-2.394	.021	-169.925	-14.773
	Age	-7.645	4.233	-.199	-1.806	.077	-16.156	.866

Psychological impact on ART delay

Our first result showed that a trend is seen on couples' agreement on the questionnaire administration and the second embryo transfer delay. The presence of both partners answers was correlated with a lower embryo transfer delay. This finding can be reassumed in a combination of three factors: the ART delay, the presence of stress, and a dyadic coping approach. The dyadic coping approach is a term which refers to the ability of both partners to deal a potential stressful situation with strategies relying in their couple, with different approaches. In the previous literature, different examples have been proposed of positive effects when considering the dyadic approach on infertility issues. First, Monirian *et al.* recently showed the effectiveness of couples coping enhancement counselling on stress for infertile couples. As the dyadic coping showed

an increase, the stress of both women and men decreased [12]. Moreover, different approaches have been proposed for evaluating the effectiveness of dyadic coping when dealing with stress factors in the infertility path, of which we recently proposed a new investigative design developed during the SARS-CoV-2 pandemic [13]. When linking together a dyadic approach to the deal of stress and the ART delay, we should consider a recent randomized controlled study by Song *et al.* which presented results limiting the delay of frozen thawed embryo transfer in terms of ongoing pregnancy rate. Moreover, they warranted on the indiscriminate application of a delayed embryo transfer, especially when high stress is perceived [14]. Subsequently, we performed a Spearman correlation between the four sections investigated: the personal, social, marital status, and sexual impact session. Initially, we found a positive correlation on

the intra-section scores, which was expected. However, we deepened our analysis evaluating the inter-section links and found that the marital status section showed a different correlation from the other sections. Slight differences were seen for single questions. On this regard, the psychological impact of stress deriving from the infertility path has been studied for years, in order to find possible correlations with biological outcomes and the best efficient method to reduce it in order to increase quality of life [15]. Previous studies have investigated the correlation between infertility factors and personal, social, marital and sexual factors. First, the quality of life in infertile couples have been directly associated with self-esteem, social support, sexual satisfaction, and marital satisfaction [16]. According to our results, the marital status showed a different correlation with other issues, which has been previously described when studying the correlation between infertility impact on psychological wellbeing [17].

On this scenario, we aimed to find predictors for ART delay. Initially, when considering the single answers on questionnaire administration we found the following predictors: a lower number of frozen thawed embryos, the presence of health issues, and a positive correlation with the score of three questions addressing the social impact. To continue with, we analysed predictors for ART delay based on couples' agreement to the questionnaire. We found as predictors: a lower number of frozen thawed embryos, the concordance on marital status section, and a positive correlation with the score of two questions addressing the social impact, in case of concordance. Moreover, a single question on the marital status section provided a predictive model in case of concordance. Despite the fact that the psychological impact of infertility has been previously studied, we first tried to find predictors for ART delay, based on a couples' questionnaire during the SARS-CoV-2 pandemic. On this regard, we tried to address an infertility issue which is every day more debatable: the time to pregnancy outcome. Accordingly, a growing interest on maximizing IVF efforts in reducing attempts delay is undeniable [18, 19]. This trend is probably due, in our opinion, to an inverse logarithmic success rate of IVF procedures which is, accordingly, progressively decreasing. Indeed, the time to pregnancy can be reduced maximizing the number of IVF procedures, especially embryo transfers. In this scenario, our study tries to address the presence of eventual predictors which could help increasing our next ART outcomes.

The SARS-CoV-2 pandemic impact

Furtherly, we analysed the reasons for ART delay, specifically designed in our questionnaire, and the SARS-CoV-2 impact. At the first sight, the health reasons were responsible for the greater second embryo transfer delay in terms of days. External reasons and the SARS-CoV-2 accounted for the least. Moreover, when considering the eventual SARS-CoV-2 infection in one member of the couple, which was responsible for at least a period of quarantine, the ART delay accounted for only 16 days, showing a low impact. On the contrary, the worldwide effect of SARS-CoV-2 pandemic has been directly determinant on IVF procedures delay [20]. However, previous studies searched for possible psychological connector which could distinguish the SARS-CoV-2 distress to the infertility stressors. In our scenario, we aprioristically distinguished the SARS-CoV-2 impact to other reasons, in a population which have dealt with the pandemic for two years, when possible viral fear factors have vanished with the worldwide vaccination. Indeed, when referring to studies published before the vaccination period, most patients had tests or treatments postponed with a development of stress, worry, and frustration risen especially from the uncertainty given from the IVF center closure [21, 22]. With the advent of therapies and vaccination, the reopen of IVF centre, and the reduction of the SARS-CoV-2 worldwide lockdown, the stress factors associated gradually decreased. For this reason, the actual interest relies more on the possible IVF outcomes after SARS-CoV-2 vaccination, rather than the infection itself on the ovarian stimulation. On this regard, a recent study on 240 women provided evidence about the lack of correlation on IVF outcomes [23]. However, a recent study about the SARS-CoV-2 vaccination (first dose) showed greater outcomes after fresh embryo transfer for women receiving the vaccine after at least 60 days [24]. Of outmost importance, we found no predictors in SARS-CoV-2 questions suggesting the lack of influence of SARS-CoV-2 pandemic in our centre ART delay. This trend is quite opposite in literature and more debatable as follows: the SARS-CoV-2 pandemic increased stress and grief in infertile couples which empowered the ART postponement stress [25, 26]. Our opinion relies on focusing on the reduction of ART delay specifically targeting the infertile population experiencing more distress and grief. The SARS-CoV-2 pandemic, fortunately, has a minimal hamper on stress of infer-

tile couples which can be considered as the queue of a global pandemic impact. To stress the importance of this study for clinical practice, we should consider the following items. First, SARS-CoV-2 showed no influence on our IVF centre treatments delay. This finding could be reassuring, since clinicians could not expect a negative influence on the ART schedules in case of SARS-CoV-2 infection in one or both partners. Secondly, clinicians could find in our study some relationship insight for a delayed embryo transfer. In this scenario, the most useful piece of information could rely on the fact that the more the frozen embryos, the lower the drop-out and the time lost in ART.

Strengths and limitations

Our study provides new data and evidence about the relationship between the SARS-CoV-2 infection and the delay in ART procedures. Specifically, the ART drop-out, a new target in IVF centre is addressed with a specific questionnaire. Indeed, the tri-chromic relationship between the ART drop-out, the questionnaire, and the SARS-CoV-2 infection in our large population is the most reliable evidence of our study. Although the peculiarity of the analysis, our study presents some limitations. First, we enrolled a little population which could have hampered the results. However, this low number was related to the strict inclusion criteria, which tailored our outcomes. Moreover, since the main time interval of our study was related to SARS-CoV-2 infection, we enrolled only people undergoing ART treatments from the 2020/2021 years.

In addition, a pre-selection bias occurs since we enrolled only patients who answered our questionnaire. Probably, we included only people with positive feedback about our centre who aimed to continue with ART treatments. Moreover, we included only people with a partner (at the moment of the questionnaire administration). This fact was strengthened since some people who refused to take part to the questionnaire presented a negative centre experience or a divorce occurrence as justification.

CONCLUSIONS

Our study provides evidence about the presence of predictors for embryo transfer delay in a population dealing with infertility treatments during the SARS-CoV-2 pandemic. Accordingly, the pandemic factor showed a lack influence on the postponing of treatments. The number of fro-

zen thawed embryos, health issues, and the concordance on marital status questionnaire section resulted in predictors for embryo transfer delay.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

G.B.: Conceptualization, writing – original draft, writing – review & editing. R.V.: Data curation, writing – review & editing. M.P., L.P.: Data curation. V.S.V., A.S., M.C., E.P.: Supervision, validation.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

All procedures performed in studies involving human participants were in accordance with 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.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Data sharing

All data are provided within the document.

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SUPPLEMENTS

Appendix 1. *Description of psychosocial measures used to evaluate the impact of an infertility diagnosis [7] which was partially modified according to the aim of the study.*

GROUP A: Personal Impact

Because of your fertility problems, how often have you felt (0 Never, 10 Very Often):

A1: Not in control of your life?

- A2: That you might miss something important in life?
- A3: That you couldn't meet your life goals?
- A4: That you must have done something to deserve these problems?
- A5: Defective?

Total score determined by sum of 5 questions divided by 50 and multiplied by 100. High scores represent great impact.

For our modified version, we valued these questions as follow: low score included values 0-3, medium score included values 4-6, and high score included values 7-10.

GROUP B: Sexual Impact

What effect have your fertility problems had on your sexual relationship? (0 Strongly Disagree, 4 Strongly Agree)

- B1: * I find I've lost my enjoyment of sex because of our fertility problem.
- B2: * I feel just as attractive to my partner as before our fertility problem (reverse-scored).
- B3: * I don't feel any different from other members of my sex because of our fertility problems (reverse-scored).
- B4: * I feel that I've failed at sex because I can't get my partner pregnant.
- B5: * During sex, all I can think about is wanting a (another) child.

Total score determined by sum of 5 questions divided by 28 and multiplied by 100. High scores represent great impact.

*Questions taken from Fertility Problem Inventory (Newton CR, Sherrard W, Glavac I. The Fertility Problem Inventory: measuring perceived infertility-related stress. *Fertil Steril.* 1999;72(1):54-62. doi: 10.1016/s0015-0282(99)00164-8.)

For our modified version, we valued these questions as follow: low score included values 0-33, medium score included values 34-66, and high score included values 67-100.

GROUP C: Marital Impact

What effect have your fertility problems had on ... (0 Very negative effect, 4 Very positive effect)

- C1: How much you enjoy the time you spend with your partner? (reverse-code)
- C2: How often you and your partner have disagreements and arguments? (reverse-code)
- C3: How satisfied you are with your partner? (reverse-code)
- C4: How satisfied you are with your relationship in general? (reverse-code)
- C5: How stable your relationship is? (reverse-code)
- C6: How much you feel that you and your partner are a team? (reverse-code)
- C7: How close you feel to your partner? (reverse-code)

Total score determined by sum of 7 questions divided by 28 and multiplied by 100. High scores represent great impact.

For our modified version, we valued these questions as follow: low score included values 0-33, medium score included values 34-66, and high score included values 67-100.

GROUP D: Social Impact

How often do you feel uncomfortable (0 Never, 10 Very Often)

- D1: with family members because they ask when you and your partner are going to have a (another) baby?
- D2: with family members because they give you unwanted or unhelpful advice about having a (another) baby?
- D3: with family members because they minimize what you are going through to try to have a (another) baby?
- D4: with family members because they make insensitive comments about your fertility problems or getting pregnant?
- D5: with friends because they ask when you and your partner are going to have a (another) baby?

- D6: with friends because they give you unwanted or unhelpful advice about having a (another) baby?
- D7: with friends because they minimize what you are going through to try to have a (another) baby?
- D8: with friends because they make insensitive comments about your fertility problems or getting pregnant?
- D9: when your friends talk about their pregnancies or their children?
- D10: around friends or family members who are pregnant or who have new babies?
- D11: with co-workers because they know about your fertility problems?
- D12: around babies or young children in your extended family?

How often do you feel that ... (0 Never, 10 Very Often)

- D13: your partner doesn't understand your feelings about having a (another) baby?
- D14: your partner doesn't understand what trying to have a (another) baby is like for you?
- D15: you can't talk to your partner about having a (another) baby?
- D16: your family doesn't understand what trying to have a (another) baby is like for you?
- D17: you can't talk to your family about your problems having a (another) baby?
- D18: your friends don't understand what trying to have a (another) baby is like for you?
- D19: you can't talk to your friends about your problems having a (another) baby?
- D20: people avoid talking to you about your problems having a (another) baby?
- D21: you don't have anything in common with your friends who have not had fertility problems?
- D22: being around some of your friends because of your problems having a (another) baby?

How often have you avoided ... (0 Never, 10 Very Often)

- D23: being around some members of your family because of your problems having a (another) baby?
- D24: going to holiday gatherings because of your problems having a (another) baby?
- D25: going to other social gatherings because of your problems having a (another) baby?

Total score determined by sum of 25 questions divided by 250 and multiplied by 100. Higher score represents great impact.

For our modified version, we valued these questions as follow: low score included values 0-3, medium score included values 4-6, and high score included values 7-10.

Moreover, we administered the following modifications:

We added two questions addressing the SARS-CoV-2 pandemic impact on couples' perspective and ART path and one question addressing the reason of couples' delay on pursuing the second embryo transfer, specifically targeting the health issues, logistic problems, spontaneous pregnancies (Section 1). The questionnaire comprised a list of possible motivations that couples could sign for the delay for the second embryo transfer. Moreover, patients could write their personal motivation more specifically. The provided reasons for delay were: moving house, work motivations, family reasons, health reasons not related to the reproductive sphere, health reasons related to the reproductive sphere, ART in one other IVF centre, spontaneous pregnancy, other. These reasons were subsequently grouped in two areas: health reasons and external reasons (*i.e.*, from the couple itself). The health reasons group comprised couples who indicated health reasons both related to the reproductive sphere and to other areas, as well as those couples who have specified in the "other" section the type of disease or the operations to which the members of the couple underwent (or had to). On the other side, in the external reasons group there were comprised all other reasons, included the spontaneous pregnancies. In addition to these group of reasons, a new third group specifically related to the SARS-CoV-2 infection was created. This group comprised every event related to the SARS-CoV-2 which was responsible for a delay in the second embryo transfer.

1. We added two questions addressing the patients' infection by and vaccination from SARS-CoV-2 (Section 2).
2. We eliminated five questions regarding the social impact aspects because we considered them repetitive for our purposes (D9, D11, D12, D24 and D25).
3. We considered partners' answers concordant if they were both low, medium or high score or in different score but with maximum 1-point difference for group A and D questions and maximum 15 points question scores ranging 0-100 on total.