

SHORT COMMUNICATION

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Spontaneous pregnancies among infertile couples during assisted reproduction lockdown for COVID-19 pandemic

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Abstract

Background: The worldwide spread of the SARS-CoV-2 infection has profoundly affected all aspects of human life, with tangible consequences in several contexts, including reproduction. However, evidences on the inter-relation between psychological distress and reproductive medicine are still conflicting.

Methods: The national lockdown imposed in Italy in March-May 2020 and the consequent assisted reproductive techniques (ART) activity blockage allowed to evaluate the conception ability of couples who suffered the postponement of ART cycles. In particular, we collected anamnestic, anthropometrical and demographic data of those women attending ART straddling the lockdown period attending to the Fertility Centre of Reggio Emilia.

Results: Among the 431 couples recalled to reschedule ART cycles, 34 couples (7.9%) obtained a spontaneous pregnancy during the lockdown. Comparing spontaneously pregnant to non-pregnant women, the pregnant group resulted younger ($P = 0.009$) and with a shorter infertility history ($P = 0.029$). Interestingly, the sexual activity frequency was significantly higher in pregnant women compared to non-pregnant ones ($P < 0.001$). In a multivariate logistic analysis, number of sexual intercourses *per* week and the infertility history duration were significantly related to pregnancy ($P < 0.001$ and $P = 0.030$, respectively). In addition, the application of neural network technology including data about women age, body mass index, infertility duration, weekly sexual intercourses and infertility causes allowed to correctly classify pregnant women with an accuracy of 92.7%.

Conclusion: The high pregnancy rate observed in a very short time-frame interval probably revealed an under-explored cause of idiopathic infertility, that is the frequency of sexual intercourses, resulting the best predictive variable on achieving a spontaneous pregnancy. This factor is commonly under-investigated during the anamnestic workup of infertile couples. Clinicians involved in ART should better investigate the sexual habits of infertile couples, with the aim to correctly apply ART to those couples who really need it, avoiding unnecessary over-treatment for those couples able to conceive spontaneously.

KEYWORDS

assisted reproduction, COVID-19, national lockdown, pregnancy rate

1 | INTRODUCTION

The beginning of 2020 was characterized by the spread of the SARS-CoV-2 infection,¹ that prompted the World Health Organization (WHO) to declare the coronavirus disease (COVID)-19 a global public health emergency. In Italy, a national lockdown was declared under government provision starting from 9 March 2020, limiting the population displacements, with the attempt to stem the fast viral dissemination. This constrained national lockdown lasted until 4 May 2020, accompanied by a climate of fear and insecurity² potentially affecting individual psychological status. Indeed, it is well established that actions aimed at limiting individual freedom, that is lockdown restrictions, could impair psychological balances, inducing behaviour anxiety, fear of the future and panic and exacerbating adaptation disorders and depression.³ Accordingly, a recent survey conducted in China on 1210 subjects highlighted the pandemic consequence on psychological health, showing a severe anxiety syndrome in the 53.8% of the interviewed cohort.⁴

In this context, couples planning to have a child were not exempt from these psychological sequelae. Indeed, a relevant number of couples in search of pregnancy in the pre-COVID era abandoned the intention during the lockdown, fearing of the future economic difficulties and the unknown viral consequences on the foetus.⁵ Moreover, according to nationally imposed restrictions on non-urgent medical activity, all national and international societies for reproductive medicine advised to stop and postpone all assisted reproductive technique (ART) cycles. Thus, infertile couples attending the assisted fertilization centres unintentionally interrupted their ART paths with the uncertainty regarding the activity restart. Thus, not surprisingly, as reported in a large Italian survey, both the COVID-19 pandemic per se and the ART activity stoppage contributed to generate high distress in infertile couples interviewed.⁶

The psychological health of infertile couples has clinical implications in reproductive medicine, since the psychological stress was demonstrated to affect sexual health and couple stability.⁷ However, the real impact of psychological stress on couple infertility in terms of pregnancies obtained is largely under-investigated in the literature. A possible clinical measure of the couples' psychological distress could be the frequency of sexual intercourses. However, conflicting evidences are currently available concerning the interrelation between psychological health and sexual practices. Indeed, two Italian surveys suggested that the lockdown-related anxiety was associated with a reduction in sexual intercourses *per week*.^{5,8} On the contrary, Pacchiarotti et al. reported an increased sexual activity *per week* during COVID-19 lockdown in 57 infertile couples interviewed.⁹ This result could be partially justified since couples have been forced to reinvent their habits, spending much more time at home within their own family. Moreover, men and women who feel depressed or anxious could experience an increased sexual interest inducing an increase in sexual intercourses frequency.^{10,11} Lastly, the potential low frequency of sexual activity is usually poorly considered in the management of couple infertility and its role on pregnancies failure is unclear, but probably underestimated.

With this in mind, hypothesizing that the COVID-19-related lockdown could have an impact on infertile couples, we investigated whether the recent national lockdown had any effect on spontaneous conception in couples attending ART.

1.1 | An unexpected 'bright side' of COVID-19: spontaneous pregnancy during ART lockdown

The Fertility Centre of the Department of Obstetrics and Gynaecology of Reggio Emilia (Italy) stopped 431 ART cycles during the national lockdown, according to the provisions of the Italian Institute of Health. The length of the lockdown was not known *a priori*, and it was decided according to the trend of the contagion curve, therefore scarcely predictable. Thus, couples waiting for ART cycle were postponed to a later date without further specifications. Once the non-urgent medical activity blockage has been removed, these couples have been recalled to reschedule the ART cycles suspended. We decided to evaluate this population attending ART, who have suffered the interruption of fertilization paths because of the SARS-CoV-2 pandemic. In particular, we collected anamnestic, anthropometrical and demographic data of those women attending ART straddling the lockdown period. Male partners had not been evaluated yet by an andrologist, thus no infertility treatment for the male factor was ongoing during the lockdown. Usually, anthropometric and semen data of the male partner are collected only when the couple is close to ART initiation and exit the waiting list. Thus, male age was available for the 62% of the cohort (267 couples) and semen analyses for the 12% of the series (51 patients). The mean men age was 39.6 ± 4.1 years. The mean women age was 37.6 ± 4.4 years, with a mean body mass index (BMI) of 23.9 ± 4.8 kg/m². The average duration of couple infertility was 3.5 ± 2.8 years, while an exclusively female causal factor was observed in the 23.7% of cases (102 couples), an exclusively male one in the 32.7% (141 couples), a coexistence of male/female factor in the 18.6% (80 couples) and an idiopathic form in the 25.1% (108 couples). The male factor of infertility was not evaluated in all couples; thus, this definition came from the anamnestic evaluation of the couple.

Interestingly, 34 couples (7.9%) obtained a spontaneous pregnancy during the COVID-19 lockdown. Comprehensively, these couples presented a female infertility factor in the 26.5% of cases (9 couples), a male factor in the 29.4% (10 couples), a male/female factor in the 11.8% (4 couples) and idiopathic infertility in the 32.4% (11 couples). Comparing spontaneously pregnant to non-pregnant women (Table 1), the mean age of the woman resulted significantly lower in the pregnant group ($P = 0.009$). Similarly, the infertility history was shorter in pregnant patients ($P = 0.029$). On the contrary, no differences were detected comparing BMI ($P = 0.164$) or the infertility causes ($P = 0.583$) (Table 1). Data were not normally distributed and statistical comparison was performed using Mann-Whitney *U* test. In order to better understand this unexpectedly high spontaneous pregnancy rate, we asked the women how often they had unprotected sexual intercourses during the lockdown. The

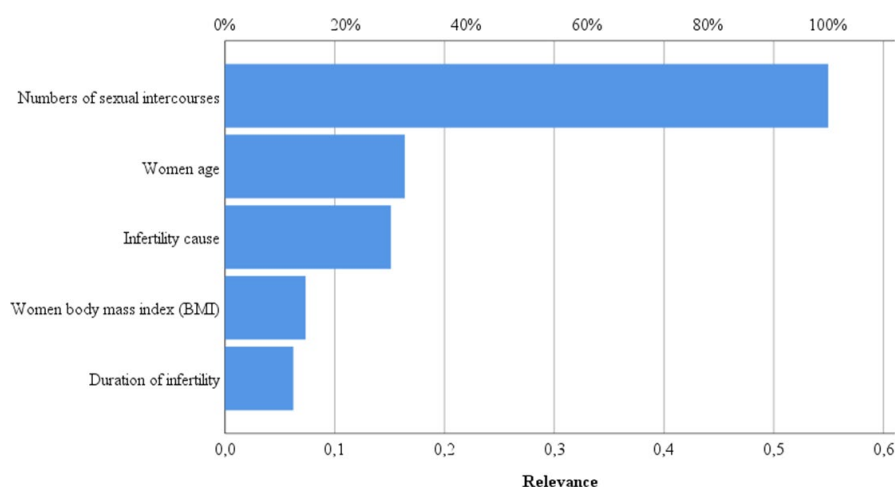
TABLE 1 Characteristics of women stratified by pregnancy occurrence

	Pregnant group (n = 34)	Non-pregnant group (n = 397)	P value
Women age (years) (mean±SD)	35.7 ± 4.2	37.7 ± 4.4	<i>P = 0.009</i>
Women BMI (kg/m ²) (mean±SD)	22.7 ± 4.2	24.0 ± 4.9	<i>P = 0.164</i>
Infertility duration (years) (mean±SD)	2.4 ± 1.6	3.6 ± 2.8	<i>P = 0.029</i>
Infertility cause (n, %)	<ul style="list-style-type: none"> • Female factor (9, 26.5%) • Male factor (10, 29.4%) • Male/female factor (4, 11.8%) • Idiopathic (11, 32.4%) 	<ul style="list-style-type: none"> • Female factor (94, 23.7%) • Male factor (130, 32.7%) • Male/female factor (77, 19.4%) • Idiopathic (96, 24.2%) 	<i>P = 0.583</i>

Bold italic values express statistically significant difference.

Abbreviations: BMI, body mass index; SD, standard deviation.

FIGURE 1 The relevance of each covariate and cofactor included in the neural network is represented as the result of the neural network analysis.



frequency of sexual activity was significantly higher in pregnant women compared to non-pregnant ones (3.6 ± 1.1 versus 1.9 ± 0.8 sexual intercourses/week, $P < 0.001$).

Considering all the variables together (ie women age, BMI, duration of infertility, number of sexual intercourses *per* week and infertility aetiology) in a multivariate logistic analysis, we highlighted that the infertility history duration and the sexual intercourses frequency were significantly related to pregnancy ($F = 4.8$, degrees of freedom=1, $P = 0.030$ and $F = 81.6$, degrees of freedom=1, $P < 0.001$, respectively). In details, this analysis was performed setting pregnancy (categorical data) as the dependent variable, and all other available data as either covariates or cofactors. Moreover, we applied neural network technology (using Bayesian models), considering obtained pregnancy as dependent variable, women age, BMI, infertility duration and weekly sexual intercourses as covariates and infertility causes as factors. The model was trained using the 70.3% of the entire dataset randomly selected and it was further validated using the remaining 29.7% of data. The neural network analysis was able to correctly classify pregnant women with an accuracy of 92.7%. In particular, the analysis confirmed that the number of sexual intercourses is the main predictive factor of spontaneous pregnancy, explaining the 55% of the data series (Figure 1).

2 | DISCUSSION

During the COVID-19 lockdown, an increase rate of spontaneous pregnancies was observed in infertile couples attending a third-level ART centre in Northern Italy. This result is only partially unexpected, since several authors previously reported a relevant increased chance of spontaneous conception during the waiting time requested for each ART cycle.¹² Although we have no firm data about the spontaneous pregnancy rate during the waiting time for ART in our Centre, we were puzzled by the unexpectedly high number of pregnancies upon recall for ART rescheduling after lockdown, which prompted the present investigation. Matorras et al. highlighted a spontaneous pregnancy rate of 7.6%, evaluating 285 infertile couples attending ART in a time-frame interval of two years.¹³ A recent meta-analysis of nine studies considering infertile couples attending ART reported an overall spontaneous pregnancy rate of 9.6% during an average five months of waiting.¹⁴ The spontaneous pregnancy rate extrapolated from our casuistry (ie 7.9%) results comparable to those previously reported. However, unlike other studies, our results are obtained in only two months of observation, corresponding to the duration of the national lockdown. This unexpected high pregnancy rate probably revealed one of the under-explored causes of idiopathic infertility during the

anamnesic workup, that is the frequency of sexual intercourses. Indeed, this factor resulted significantly higher comparing the pregnant women group to the non-pregnant, as well as the best predictive variable on achieving a spontaneous pregnancy. Available data do not allow us to attribute or not this increase in sexual intercourses frequency to the couples' psychological state. Indeed, considering the absence of measurable data about psychological health in these population, we are still unable to clarify the inter-connection between the psychological stress experienced by couples during the COVID-19 blockage and the frequency of sexual activity. However, our opinion is to include the evaluation of the sexual intercourses frequency in the diagnostic workup of couple infertility. Moreover, a psychological support during ART should be planned, considering the many available evidences about the potential psychological impact of stress on reproductive medicine, also in a non-pandemic era.

In our case series, younger women with a shorter infertility history show higher chances of achieving spontaneous pregnancy. This phenomenon is clinically obvious and expected, but the national lockdown allows us to make some additional considerations on this aspect. The impact of women age and the infertility history duration on fertility outcomes is so relevant that it emerges even from a short observation period (ie two months). Moreover, the application of more complex statistical analyses, such as logistic regression and neural network analyses, allowed the creation of a statistical model able to predict spontaneous pregnancies with a 92.7% of accuracy, considering only few clinical variables. Interestingly, the infertility aetiology resulted not involved in the calculated prediction of spontaneous pregnancies. This statistical model requires validation and is potentially extremely relevant for future clinical and research applications.

Despite the short observation period (two months), the large sample size of women evaluated attending to a single ART centre constitutes a point of strength of our study. However, the absence of a control group represents the most important limit.

In conclusion, our opinion is that the national lockdown allowed to increase the knowledge about an underestimated factor of couple infertility and to characterize it in a timely manner with an accurate statistical analysis. Thus, clinicians involved in ART should better investigate the sexual habits of infertile couples, such as the number of sexual intercourses *per week*, or any pathological condition potentially obstructs the efficacy of sexual intercourses, such as vaginismus, dyspareunia or anejaculation. In addition, increasing the frequency of sexual activity should be promoted regardless of the infertility aetiology, especially in case of lower women age and of a shorter infertility duration. The increased knowledge about this aspect in reproductive medicine could help to identify those couples able to conceive spontaneously, avoiding unnecessary over-treatment, and to correctly apply ART to those couples who really need it.

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CONFLICT OF INTEREST

All authors have no potential conflicts of interest.

AUTHOR'S CONTRIBUTION

Conceptualization: GS, MTV, DS; patients' enrolment: DM, MTV, LA; data collection: DM, MTV, LA; statistical analysis: GS, DS; draft the article: GS, DS; revision of the article: DM, MTV, LA, GS, MS and DS.

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