Assisted reproductive technology treatments and quality of life: a longitudinal study among subfertile women and men

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Abstract

Purpose Quality of life (QoL) may represent a comprehensive indicator for the assessment of the psychological impact of complex clinical conditions, such as infertility. Infertile women have a worse QoL compared to both infertile men and non-infertile controls. However, the initial phases of infertility treatments have been frequently investigated using cross-sectional study designs. This prospective longitudinal study aimed at assessing the health-related QoL change across different phases of assisted reproductive technology (ART) treatments in subfertile women and men.

Methods Eighty-five subfertile women and men undergoing ART cycles were assessed at the beginning of the ovarian stimulation, during oocyte retrieval before discharging, and around 14 days after the embryo transfer. QoL was assessed through the Short Form 36.

Results Irrespective of the cause of infertility, work status, and age, QoL levels decreased from the first to the third assessment, and women scored significantly lower than men to each QoL indicator. Additionally, a higher number of previous ART failures had a negative impact on QoL, irrespective of gender and the phase of treatment. ART outcome marginally affected women's QoL across time.

Conclusion Infertile women have a worse QoL throughout all phases of ARTs compared to men, and this difference

increases in infertile patients with more than one previous ART failure.

Keywords Assisted reproductive technology · Infertility · Quality of life · Women · Men · Longitudinal study

Introduction

In Europe, the overall number of cycles of medically assisted reproduction treatments, including assisted reproductive technology (ART) programs, has continued to increase year by year up to 2010 [1]. According to the last report of the Italian National Health Institute about infertility and ARTs [2], it appears that in Italy, in 2013, the number of cycles per million population is lower than the European average. Nevertheless, this figure is higher compared to single countries such as the UK and Germany [2].

The great distress experienced by couples undergoing ARTs [3], particularly by women [4–7], can be considered as the consequence of both the diagnosis of infertility, which represents a critical life event per se, and the extensive and emotionally challenging methodologies which typify these medical procedures. The serious emotional burden experienced through the course of ARTs [8, 9] leads around 23% of couples to prematurely give up with treatments [10].

For these reasons, recent guidelines from the European Society of Human Reproduction and Embryology (ESHRE) highlight the importance to incorporate psychosocial assistance into clinical practice for infertility [11]. According to several authors [12, 13], infertility care should particularly take into account the levels of patients' quality of life (QoL), as QoL is believed to be a relevant way to comprehensively assess the impact of complex clinical conditions, such as infertility, on individuals [14].

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The literature shows that the experience of ARTs significantly affects patients' QoL [9, 13, 15, 16], given also its negative impact over several areas of individual functioning, including marital relationship [17, 18], sexual satisfaction [19–21], psychosocial well-being [22, 23], depression and anxiety [24, 25]. Additionally, findings from a recent review [13] showed that overall, subfertile women have lower QoL scores compared to subfertile men and lower scores on mental health and social functioning when compared to normative data. However, the authors also concluded that little is still known about the impact of infertility on the QoL of subfertile men and women [13].

Though some studies focus on the determinants of a lower QoL during infertility treatments, including unemployment status, low income, longer duration of infertility, previous ART treatments and advanced age [26–29], most of them are mainly focused to the initial phase of the medical procedure using cross-sectional study designs. In fact, specific moments of the treatment, such as the beginning of ovarian stimulation (the moment in which patients actually start their ART treatment) and the oocyte retrieval (that is consisted in the first real application of bio-medical technologies in the treatment), seem to be closely related to increased levels of depression and anxiety [8, 9]. Moreover, the potential effects of a history of repeated failures in conceiving through ARTs have been systematically neglected.

Nevertheless, a number of studies that examine the QoL of infertile patients longitudinally do exist [30, 31]. For example, Domar and colleagues examined the QoL of women pre- and post-infertility treatment, prior to realization of the pregnancy outcome. The authors demonstrate an improvement of QoL but only for those women who underwent a cognitive coping and relaxation intervention [30]. In another recent study, fertility-related QoL was measured over a 3-month period and was associated with decisional regret as to whether continue or not with ARTs after a failed IVF cycle [31]. However, both studies focused on women only.

In light of the foregoing considerations, the present study aimed to investigate the levels of patients' health-related QoL throughout the ART treatment process and to differentiate the results, taking into account gender as well as the number of previous ART failures. In particular, considering available data on subfertile women's QoL [13], we tested the hypothesis that during a complete ART cycle, women show lower levels of QoL compared to men and that the number of previous ART failures in conceiving influences more women's QoL than that of men. Additionally, we aimed to investigate trajectories of change in QoL during ARTs. Indeed, given that the period of time between embryo transfer and treatment outcome seems to be the time of greatest distress for many women undergoing ARTs [32], we expected a decrease in women's QoL levels from the beginning of the ovarian stimulation to the period preceding the pregnancy test.

Materials and methods

Participants

Patients undergoing ARTs were recruited at the Centre of Reproductive Medicine and Surgery of the Santa Maria Nuova Hospital of Reggio Emilia (Italy) between September 2007 and June 2011. ART treatments were covered by the Italian National Health System, which offers public provision of free health care. Both in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles were included. The lack of understanding of the Italian language and the presence of any complication during the ART cycle were considered as exclusion criteria. Complications during ART cycle included any deviation from common clinical course of the cycle, such as risk of ovarian hyperstimulation syndrome (OHSS), a poor ovarian response (less than three follicles), oocyte retrieval complication (i.e., peritoneal bleeding, pelvic sepsis, or abscesses) [33]. No patient underwent psychological counseling, neither before nor during the treatment.

Ethics

The study was not submitted to the ethics committee because the procedures included in the protocol did not require any intervention or variation from the common clinical practice, and for this kind of non-interventional study, the submission in 2007 was not mandatory according to the Italian law. The study was conducted in accordance with the Helsinki Declaration. At enrollment, all patients (women and their partners) had written information about the study protocol, the specific consent was obtained, and a written informed consent to use non-sensitive data for research was signed.

Data collection

A researcher formally contacted by telephone all patients who met the inclusion criteria in order to explain the study protocol and to ask for participation. Men and women were included in the study only after a formal written informed consent was obtained.

At enrollment, demographic and clinical (psychological and medical) data were recorded in both male and female patients. At each assessment point, participants received an envelope containing the questionnaires and a prepaid envelope for returning the completed material. The first envelope was sent at the beginning of the ovarian stimulation and the second during oocyte retrieval before discharging, whereas the last was sent 14 days after the embryo transfer, but before knowing the formal result (positive or negative) of the β -HCG assay. Patients were recommended not to check independently for a possible pregnancy before 14 days from the embryo

transfer have passed, in order to avoid possible false negatives.

Measurement instruments

Sociodemographic variables (such as age, level of education, and profession) were assessed by means of an ad hoc questionnaire, including also specific questions on a possible history of relevant psychiatric problems. Besides, a simple self-report measure (General Health Questionnaire, GHQ-12, [34]; Italian validation by [35]) was used to evaluate the presence of mental health problems and as a more general measure of psychological well-being. Data on GHQ-12 will not be presented here, as this is not the main aim of the study. Another manuscript is under preparation specifically focusing on the GHQ-12 scores and their influence on QoL levels in women and men.

Clinical data, including the presence and number of previous pregnancies, the presence and number of previous failed ART treatments, and the cause of infertility, were collected from medical records.

QoL was measured through the Short Form 36 (SF-36) [36] using the Italian version [37]. The SF-36 comprises 36 items and provides scores to eight dimensions of physical and mental health-related to QoL: physical functioning (PF), i.e., extent to which health interferes with performance in everyday physical activities (e.g., carrying groceries, climbing stairs, and walking); role physical (RP), i.e., a degree to which health interferes with usual daily activities such as work, housework, or school; bodily pain (BP), i.e., intensity of bodily pain and extent to which it interferes with normal work; general health (GH), i.e., current evaluation of personal health; vitality (VT), i.e., a degree to which a person feels full of energy or worn out and tired; social functioning (SF), i.e., an extent to which health interferes with normal social activities like visiting friends during the past month; role emotional (RE), i.e., a degree to which emotional problems impede everyday activities such as work; and mental health (MH), i.e., an extent to which a person feels a positive or a negative mood. Scores range from 0 to 100, with higher scores at each dimension indicating better QoL. In the present study, Cronbach's alpha values for the dimensions of the SF-36 ranged between 0.70 and 0.87.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 21, for Windows (NY, USA). Pearson's chi-square test and univariate analysis of variance (ANOVA) were performed to test for differences in the demographic and clinical characteristics of the sample. Repeated measures ANOVA was used to test the differences between men and women in QoL over the three

time assessments, controlling for the number of previous failures in conceiving through ARTs (i.e., none, only one, more than one). Potential differences related to the cause of infertility (male, female, both, and unknown) and to the ART program (IVF vs. ICSI) were also checked by means of ANOVAs. Although the last assessment was performed before giving the formal result (positive or negative) of the β -HCG assay to patient, as a further control, the role of treatment outcome was investigated. To this end, generalized estimating equation analyses were performed for each dimension of the SF-36 to explore the interactions of gender, time of assessment, and treatment outcome, controlling for any demographic difference emerged in the sample.

A *P* value less than 0.05 was considered statistically significant.

Results

Characteristics of the sample

The final sample included 85 men and 85 women. In 42.5% of cases, infertility was due to a male factor; in 27.6%, due to a female factor; and in 16.1%, due to both male and female, and 13.8% of patients suffered from unexplained infertility. Additionally, 36.5% of patients reported no previous ART attempts, 20.6% only one unsuccessful attempt, and 42.9% more than one attempt. The ART cycle was successful for 27.7% of the sample.

The main demographic characteristics of the final sample are shown in Table 1. Except for age, no significant differences between men and women for demographic variables were found (all *P* values >0.05). None of the patients reported to have suffered of a relevant psychiatric problem in the past years.

SF-36 dimensions according to gender, time of assessment, and number of previous ART attempts

Mean values and univariate ANOVA tests for each SF-36 dimension are reported in Table 2. The changes for each dimension are summarized as it follows: limitations in physical activities due to health problems (PF dimension), limitations in usual role activities due to physical health problems (RP, BP, and GH dimensions), alterations in energy and fatigue vitality (VT dimension), limitations in social activities due to health problems (SF dimension), limitations in usual role activities due to emotional health problems (RE dimension), and alterations in psychological distress and well-being (MH dimension).

For each SF-36 dimension, a significant effect of gender was always detected, with women showing overall lower

Table 1 Main demographic characteristics of the studied population

Characteristics	Men (<i>n</i> = 85)	Women (<i>n</i> = 85)	Total (<i>n</i> = 170)	<i>P</i> value
Age, years (SD)	39.8 (4.99)	36.51 (2.86)	38.15 (4.38)	<0.001
Ethnicity, <i>n</i> (%)				0.18
Italian	84 (92.1)	80 (94.2)	164 (96.5)	
Non-Italian	1 (7.9)	5 (5.8)	6 (3.5)	
Level of education, <i>n</i> (%)				0.14
Primary school	1 (1.2)	0 (0)	1 (0.6)	
Secondary school	12 (14.1)	10 (11.8)	22 (12.9)	
High school	47 (55.3)	37 (43.5)	84 (49.4)	
University	25 (29.4)	38 (44.7)	63 (37.1)	
Occupational status, <i>n</i> (%)				0.16
Worker ^a	15 (17.6)	6 (7)	21 (12.3)	
Employed ^b	52 (61.2)	60 (53.7)	112 (65.9)	
Self-employed ^c	18 (21.2)	17 (20)	35 (20.6)	
Unemployed	0 (0)	2 (2.3)	2 (1.1)	

Data reported as mean and standard deviation (SD) or number and percentage

^a Manual laborer

^b Employee for a company

^c Freelance

mean scores compared to men (Table 2). For the dimensions RE, GH, and VT, these were the only significant results.

Regarding the SF dimension, men and women with more than one unsuccessful ART attempt showed significantly lower levels of SF ($M_{T1} = 76.88$, $M_{T2} = 70.20$, and $M_{T3} = 70.38$), compared to men and women with both only one attempt ($M_{T1} = 79.29$, $M_{T2} = 80.36$, and $M_{T3} = 78.93$) and no previous attempt ($M_{T1} = 78.23$, $M_{T2} = 77.62$, and $M_{T3} = 79.44$). Additionally, Bonferroni correction for multiple contrasts revealed that, compared to men, women showed a statistically significant decrease in social functioning from T1 to T3 (for all comparisons, see Table 2).

When the RP domain was of concern, in a similar way to SF, Bonferroni correction for multiple contrasts revealed that women showed a significant decrease in RP scores from T1 to T3 compared to men.

With respect to the MH domain, men and women who underwent more than one unsuccessful cycle had the lowest MH levels at all the assessment points ($M_{T1} = 67.2$, $M_{T2} = 66.4$, and $M_{T3} = 60.2$), compared to men and women with both only one attempt ($M_{T1} = 72.9$, $M_{T2} = 69.8$, and $M_{T3} = 70.1$) and no previous attempt ($M_{T1} = 70.3$, $M_{T2} = 69.1$, and $M_{T3} = 68.4$). Additionally, a decrease in MH scores for the overall sample from T1 to T3 emerged, irrespective of both gender and the number of previous ART attempts observed (Table 2).

For the PF domain, men and women who underwent more than one unsuccessful ART treatment had the lowest MH levels at all the assessment points ($M_{T1} = 92.5$, $M_{T2} = 87.1$,

and $M_{T3} = 91.1$), compared to men and women with both only one attempt ($M_{T1} = 95.4$, $M_{T2} = 95$, and $M_{T3} = 94$) and no previous attempt ($M_{T1} = 95.7$, $M_{T2} = 95.8$, and $M_{T3} = 94.4$), irrespective of gender and time of assessment. The same result was found for the BP domain ($M_{T1} = 77.4$, $M_{T2} = 69$, and $M_{T3} = 72.3$), compared to men and women with both only one attempt ($M_{T1} = 81.5$, $M_{T2} = 81.1$, and $M_{T3} = 77.3$) and no previous attempt ($M_{T1} = 83.1$, $M_{T2} = 80.7$, and $M_{T3} = 80.9$).

At each time point, no effect (all P s > 0.05) of the cause of infertility (male, female, both, and unknown) and of the ART program (IVF vs. ICSI) was observed on QoL.

Yet, additional control on the role of treatment outcome revealed a significant result for two of the SF-36 dimensions only. Regarding PF, RP, and SF, an interaction between gender, moment of assessment, and treatment outcome emerged (Wald test(2) = 7.76, $P < 0.05$; Wald test(2) = 11.70, $P < 0.01$; and Wald test(2) = 6.09, $P < 0.05$, for PF, RP, and SF, respectively). Specifically, with respect to PF, women who underwent a successful treatment showed a further decrease in the scores at this dimension ($M_{T1} = 91.96$, $M_{T2} = 89.78$, and $M_{T3} = 82.17$) compared to women who faced a failed treatment ($M_{T1} = 93.92$, $M_{T2} = 91$, and $M_{T3} = 94.08$), whose scores improved at the third assessment. Regarding RP, a similar pattern was detected, with women whose treatment outcome was positive, showing a further decrease from T1 to T3 ($M_{T1} = 84.78$, $M_{T2} = 78.26$, and $M_{T3} = 35.87$), compared to women who faced a failed treatment whose scores improved ($M_{T1} = 88.33$, $M_{T2} = 75$, and $M_{T3} = 31.27$). Last, when SF was concerned, women who underwent a successful treatment

Table 2 Mean values and univariate ANOVA test for each SF-36 dimension

	1st assessment		2nd assessment		3rd assessment		Gender	Main effects		Number of previous attempts	Interaction
	Men (n = 85)	Women (n = 85)	Men (n = 85)	Women (n = 85)	Men (n = 85)	Women (n = 85)		Time of assessment	Gender and time of assessment		
RE	84.5 ± 30.8	70.7 ± 36.7	75.8 ± 42.8	60.1 ± 45.7	82.9 ± 29.5	60.5 ± 42	$F(1, 164) = 15.9, \eta_{\text{partial}}^2 = .09, P < 0.001$	$F(2, 164) = 2.5, \eta_{\text{partial}}^2 = .01, P = 0.08$	$F(2, 164) = 3, \eta_{\text{partial}}^2 = .04, P = 0.051$	$F(2, 164) = .48, \eta_{\text{partial}}^2 = .00, P = 0.62$	
GH	77.5 ± 13.9	69.8 ± 18.6	77.5 ± 13.8	71.2 ± 18.6	76.4 ± 19.2	70.9 ± 21.1	$F(1, 164) = 7.2, \eta_{\text{partial}}^2 = .04, P < 0.01$	$F(2, 164) = .23, \eta_{\text{partial}}^2 = .00, P = 0.79$	$F(2, 164) = .70, \eta_{\text{partial}}^2 = .01, P = 0.49$	$F(2, 164) = .28, \eta_{\text{partial}}^2 = .00, P = 0.77$	
VT	65.3 ± 13.1	59.5 ± 16.9	65.8 ± 15.6	59.6 ± 16.5	66.2 ± 18.9	54.4 ± 21.9	$F(1, 164) = 12.9, \eta_{\text{partial}}^2 = .07, P < 0.001$	$F(2, 164) = 1, \eta_{\text{partial}}^2 = .01, P = 0.36$	$F(2, 164) = 2.9, \eta_{\text{partial}}^2 = .03, P = 0.06$	$F(2, 164) = 3, \eta_{\text{partial}}^2 = .02, P = 0.051$	
SF	81.9 ± 16.3	73.8 ± 21.7	80.5 ± 19.7	69.6 ± 20.3	84.4 ± 17.6	66.7 ± 24.4	$F(1, 164) = 24.4, \eta_{\text{partial}}^2 = .13, P < 0.001$	$F(2, 164) = .78, \eta_{\text{partial}}^2 = .00, P = 0.46$	$F(2, 164) = 3.9, \eta_{\text{partial}}^2 = .05, P < 0.05$	$F(2, 164) = 3.4, \eta_{\text{partial}}^2 = .02, P < 0.05$	
RP	91.9 ± 22.3	84 ± 27.4	85.4 ± 35.2	66.6 ± 45.3	90.5 ± 21.9	64.5 ± 38	$F(1, 164) = 22.5, \eta_{\text{partial}}^2 = .12, P < 0.001$	$F(2, 164) = 5.7, \eta_{\text{partial}}^2 = .03, P < 0.01$	$F(2, 164) = 1.65, \eta_{\text{partial}}^2 = .02, P = 0.19$	$F(2, 164) = 4.4, \eta_{\text{partial}}^2 = .03, P < 0.05$	
MH	74.7 ± 14.3	64.5 ± 18.9	72.9 ± 15.9	63.3 ± 17.9	71.7 ± 19.1	58 ± 21.6	$F(1, 164) = 19.6, \eta_{\text{partial}}^2 = .11, P < 0.001$	$F(2, 164) = 3.5, \eta_{\text{partial}}^2 = .04, P < 0.05$	$F(2, 164) = 3.1, \eta_{\text{partial}}^2 = .04, P < 0.05$	$F(2, 164) = .61, \eta_{\text{partial}}^2 = .00, P = 0.46$	
PF	95.9 ± 9.3	92.6 ± 12.8	95.5 ± 16.9	88.4 ± 21.4	95.7 ± 14.3	90.2 ± 17.4	$F(1, 164) = 9.5, \eta_{\text{partial}}^2 = .06, P < 0.01$	$F(2, 164) = .86, \eta_{\text{partial}}^2 = .00, P = 0.42$	$F(2, 164) = 3.9, \eta_{\text{partial}}^2 = .05, P < 0.05$	$F(2, 164) = .65, \eta_{\text{partial}}^2 = .00, P = 0.52$	
BP	83.2 ± 19.7	77.5 ± 21.2	82.5 ± 23.8	69.2 ± 22.5	82.5 ± 20.7	70.6 ± 24.4	$F(1, 164) = 16.6, \eta_{\text{partial}}^2 = .09, P < 0.001$	$F(2, 164) = 2.4, \eta_{\text{partial}}^2 = .01, P = 0.09$	$F(2, 164) = 5.3, \eta_{\text{partial}}^2 = .06, P < 0.01$	$F(2, 164) = 2.4, \eta_{\text{partial}}^2 = .01, P = 0.11$	

Data are reported as mean ± SD

RE role emotional, GH general health, VT vitality, SF social functioning, RP role physical, MH mental health, PF physical functioning, BP bodily pain

showed a decrease in mean scores 14 days after the embryo transfer ($M_{T1} = 72.28$, $M_{T2} = 74.46$, and $M_{T3} = 61.41$), while women who underwent a failed treatment showed substantially stable scores ($M_{T1} = 75.21$, $M_{T2} = 71.46$, and $M_{T3} = 69.38$).

Analyses were rerun, controlling for the effects of age and occupation status on each SF-36 dimension. Overall, the P values of the main effects and of the interactions of gender, time of assessment, and treatment outcome did not significantly change with the inclusion of these variables in the generalized estimating equations.

Discussion

The present study showed that subfertile women who undergo ART treatments presented significantly lower QoL levels than their subfertile male partners throughout the different phases of the ART medical procedure, regardless of the cause of infertility. This result emerged across all the QoL indicators taken into account.

Such differences are in line with results from other authors [4–7] and further highlight the importance of taking into account the diverse psychological experiences of men and women undergoing infertility therapies. Moreover, our results demonstrated that subfertile women's scores to each QoL indicator were especially subjected to decrease throughout the ART treatment period, different from subfertile men, whose scores to most QoL dimensions seemed to remain stable across time (with the exception of RP and MH domains).

The present findings also suggest that the period preceding the response on the treatment outcome (14 days after embryo transfer) can be considered as a crucial moment for worsening of psychological well-being, compared to the beginning of ovarian stimulation and the oocyte retrieval, as indicated by a decrease of MH levels in both men and women. Such hypothesis seems reinforced by the fact that in our sample, the treatment outcome, which could have been potentially known by patients (i.e., by means of pregnancy test), marginally affected only women's QoL across time. The literature suggests that part of the psychological difficulties for men and women treated with ARTs relates to the cognitions and the personal beliefs regarding parenthood and childlessness [9, 38]. As patients progress through treatment phases and, subsequently, as the moment of the embryo transfer approaches, both members of the couple likely wish to achieve a common goal, they are about to come to terms with the immediate outcome of the treatment, and as a consequence, they have to take into account the considerable risk of a definitive failure. This phase gives rise to uncertainties, as it is still unknown if couples will have to adjust to pregnancy and parenthood or to cope after a negative outcome, which may imply potentially improved negative mood and feelings of distress.

Importantly, our results confirm once more that the number of previous unsuccessful ART attempts can increase the possibility of a worse sense of well-being for these patients [28, 29, 39]. Both social (SF), psychological (MH), and physical (PF and BP) dimensions of QoL seemed to be more affected by the number of failures in conceiving through ARTs, though women presented lower levels than men to each domain. Given the heterogeneity of these dimensions, such findings may indicate that the negative effects of a prolonged history of unsuccessful ART procedures impact detrimentally upon all levels of individual functioning, in line with the idea of a bio-psychosocial conceptualization of health and well-being [40].

Moreover, such results remained invariant irrespective of infertility diagnosis as well as of ART procedure. In other words and in line with already published studies where the SF-36 was used to assess QoL [41, 42], these findings seem to suggest that men and women's QoL is not affected by the cause of infertility. However, different from previous investigations, the current study examined such relationship longitudinally and in both men and women. Both ICSI and IVF treatments involve a complex and demanding regimen, and repeated treatment cycles are usually necessary to achieve pregnancy, so that clinical pregnancy rates range between 28.8 and 33.2% per treatment cycle [1]. Our results, coupled with such epidemiological data, may entail relevant clinical considerations, including the importance of properly supporting men and women both medically and psychologically during their infertility treatments, as the cumulative stress of multiple failures may represent a significant burden to their QoL.

This study had some strengths, which are worth considering. First, the use of a longitudinal research design ensured a more detailed perspective on the evolution of QoL throughout the infertility treatment. This is especially important, given that much of the current available literature on QoL in ART patients is based upon cross-sectional designs. Therefore, this study gives a stronger empirical evidence to the research focused on QoL during ART treatments, compared to the rest of the literature. Secondly, in an attempt to overcome the marginalization of men in the psychological literature on infertility [43], our sample comprised both men and women. Besides gender differences, our results emphasize the importance of considering that both couple members are implicated in ARTs and that both of them can be profoundly affected by infertility treatments, although to a different extent.

The current study had several methodological limitations, including the small sample size and the lack of both a dyadic perspective and a control group. Despite the longitudinal design, we did not collect data before the beginning of the ovarian stimulation, and such information could have improved the appraisal of the impact of the infertility treatment over patients' QoL. Finally, data were collected at T2 during oocyte

retrieval before discharging, and this might have partially biased our results because, as in such phase of the ART process, the number of eggs collected is revealed and subjects might have been influenced either positively or negatively based on whether the number met their expectation. Additionally, though in line with much of the available literature [13], in the present study QoL was assessed through a general questionnaire, rather than by means of a disease-specific scale, such as the FertiQoL [44]. Although a disease-specific questionnaire may provide more precise indications of the true impact of infertility [45], the use of a general questionnaire like the SF-36 provides an ultimately subjective evaluation of health-related QoL in general. The SF-36 is one of the most widely used questionnaires in the literature of infertility [41, 46], and it is still currently considered one of the most reliable instruments for the assessment of health-related QoL, in both general and specific clinical populations [47–49], also within the perinatal period [50, 51]. Therefore, the choice of this questionnaire may allow, for future researchers, to deepen the comparisons on QoL across different clinical populations. At the same time, we have to keep in mind that the use of self-report questionnaires may be biased per se, and it would be important to integrate data through other sources, such as interviews, patients' diaries, and data triangulation. In light of these considerations, further research is needed to improve our understanding of the psychological experience of ART men and women throughout the treatment process.

Overall, these results help in gaining a better insight into patient experiences during ARTs and reinforce once more the claim that patients have to adjust to treatment and not the opposite [52], with practical implications. Men and women undergoing IVF and/or ICSI treatment face many potential stressors, including their childlessness as well as the possibility of a negative outcome [7], with consequences on their QoL. Hence, in line with the recently published guidelines on psychosocial care during treatment for infertility [11], the results presented herein underline that health-care professionals should be available to provide psychological support to ART patients during all the phases of the medical procedure, given the emotional and physical difficulties associated with this experience. Particularly, in line with the idea of patient-centered infertility center care [53, 54], clinicians should consider that not all ART phases imply the same psychological consequences. Indeed, there are treatment stages where patients seem to be more prone to experience physical and emotional burden (i.e., prior the formal communication of the treatment outcome) and, therefore, they may require greater sensitivity and support. Although fertility treatments impact also psychological well-being of men [15], our data confirm that women are more affected by the experience of ARTs. For this reason, it is crucial to develop and

implement targeted psychological interventions which can lead to less distress and improve patients' QoL by taking into account the unique experiences of men and women.

Researchers and practitioners should take into account the specificity of each couples' infertility history, since both men and women who have already faced the stressors of multiple unsuccessful ART attempts may be more subjected to a psychological worsening. Therefore, current clinical practices should develop interventions and prevention programs where the impact of a history of unsuccessful medical treatments over patients' emotional experience, as well as gender differences, is taken into account especially during the waiting period before knowing the treatment outcome.

Author contributions F.M. contributed to the conception of the study and was responsible for the research program. F.A. contributed to the conception of the study and to the manuscript revision and participated in the critical discussion. F.A. contributed to the data analysis and participated in the manuscript drafting and critical discussion. M.P. participated in the study conception, data collection, and critical discussion. S.P. contributed to the manuscript revision, participated in the critical discussion and in manuscript drafting, and gave the final approval of the version to be published. G.B.L.S. participated in the study design and gave the final approval of the version to be published.

Compliance with ethical standards The study was conducted in accordance with the Helsinki Declaration. All patients (women and their partners) had written information about the study protocol, the specific consent was obtained, and a written informed consent to use non-sensitive data for research was signed.

Conflict of interest The authors declare that they have no conflict of interest.

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