PSYCHOMETRIC PROPERTIES OF THE FERTIQOL QUESTIONNAIRE IN ITALIAN INFERTILE WOMEN IN DIFFERENT STAGES OF TREATMENT

Laura Volpini[a]*; Cristina Mazza[a]; Luca Mallia[b], Nino Guglielmino[c], Federica Rossi Berluti[a], Mariana Fernandes[a] & Cristiano Violani[a]

[a] Department of Psychology, "Sapienza" University of Rome, Italy.

[b] Department of Movement, Human and Health Sciences, "Foro Italico" University of Rome, Italy.

[c] U.M.R. Centre – Hera, Reproductive Medicine Unity, Catania, Italy.

Corresponding author at:

Laura Volpini, Ph.D.

Department of Psychology, Sapienza University of Rome

Via dei Marsi, 78, 00185 Rome, Italy

E-mail address: laura.volpini@uniroma1.it

Cristina Mazza, MS; Federica Rossi Berluti, MS; Mariana Fernandes, Ph.D; Cristiano Violani, Professor

Department of Psychology, Sapienza University of Rome

Via dei Marsi, 78, 00185 Rome, Italy

E-mail: cristina.mazza@uniroma1.it; federicarossiberluti@yahoo.it; mariana.fernandes@uniroma1.it; cristiano.violani@uniroma1.it

Luca Mallia, Ph.D., Associate Professor

Department of Movement, Human and Health Sciences, "Foro Italico" University of Rome, 00197 Rome, Italy

Email: luca.mallia@uniroma4.it

Nino Guglielmino, MD, Adjunct professor

U.M.R. Centre - Hera

Reproductive Medicine Unity

Via Barriera del Bosco 51-53, 95030 Catania, Italy

E-mail: angugl@alice.it

ABSTRACT

BACKGROUND: Infertility and its treatment can have a significant impact on the individual's quality of life (QoL). Fertility-specific QoL measures can be obtained through the FertiQoL (Boivin, Takefman, & Braverman, 2011), a questionnaire with six-subscales that consider different core aspects of the person's wellbeing and way of behaving during treatment.

OBJECTIVE: Examine the psychometric properties of all six-subscales of the Italian FertiQoL in a national sample of infertile women and explore the effects of the ART treatment phases on different features of fertility-related QoL.

METHOD: 323 women, in three different treatment stages, completed the FertiQoL (Diagnostic, Stimulation, Transfer). Raw data were subject to Confirmatory Factor Analysis (CFA), and a structural equation modelling was used to validate the hypothesized model.

RESULTS: CFA shows a good fit of the data to the FertiQoL hierarchical model (chi-square/df = 1.989, CFI=0.88, RMSEA=0.055). After the deletion of 2 items, all FertiQoL scales have good or more than acceptable internal consistency. SEM analysis showed that the ART treatment phase was positively associated with fertility-related QoL scores both in the Relational (β= 0.14, p<0.05) and in the Tolerability (β= =0.17, p<0.05) subscales.

CONCLUSION: All scales of the Italian FertiQoL version maintain good psychometric characteristics; Tolerability and Relational subscales are sensitive to the stage of treatment and may provide relevant information for the medical staff.

KEY WORDS: FertiQoL / Infertility / Quality of Life / Assisted Reproductive Technologies/ Stage of treatment

Word Count: 4575

Introduction

Infertility is defined as the failure to achieve a clinical pregnancy despite having regular unprotected sexual intercourse over a twelve-month period. In the past decade this has become a global public health issue (Zegers-Hochschild et al., 2017). According to the Italian National Institute of Health, infertility affects about 15%-20% of Italian couples (Istituto Superiore di Sanità, 2018).

Several studies have consistently shown that both infertility and dealing with the problem through assisted reproductive treatment (ART) may lead to emotional and psychological distress, which has a significant negative impact on the patients' quality of life (QoL) (Chachamovich et al., 2010; Greil, McQuillan, Lowry, & Shreffler, 2011; Matthiesen, Frederiksen, Ingerslev, & Zachariae, 2011; Verhaak et al., 2007). Further studies have shown that negative reactions to infertility and its treatment (Verhaak et al., 2007) affect overall life satisfaction and wellbeing (Greil, 1997; Greil et al., 2011), the successfulness of treatments (Boivin & Schmidt, 2005), willingness to continue with the treatment (Olivius, Friden, Borg, & Bergh, 2004; Smeenk, Verhaak, Stolwijk, Kremer, & Braat, 2004) and patients' treatment evaluation (Dancet et al., 2010). Moreover, infertility and its treatment may also trigger relational difficulties in couples who have to adjust to a highly stressful situation (Peterson, Newton, & Rosen, 2003). These findings indicate that assessing QoL is an important issue in reproductive medicine.

An international collaboration of experts developed the Fertility Quality of Life (FertiQoL) questionnaire (Boivin, Takefman, & Braverman, 2011) to address the need of a specific QoL measurement for women and men experiencing fertility problems. The FertiQoL differs from other existing fertility instruments because it assesses a broader concept of QoL and presents a condition-specific psychometric assessment of different cognitive, relational and emotional aspects of QoL for both men and women suffering from infertility and undergoing ART (Gameiro et al., 2015). The FertiQoL has two modules, assessing respectively Core aspects of infertility-related QoL and Tolerability and satisfaction with the treatment environment. The questionnaire has been translated and validated in numerous countries (see www. fertiqol.org), showing good overall psychometric characteristics (e.g. Aarts et al., 2011; Sexty et al., 2018). It has also demonstrated good convergent validity with measures of depression, anxiety and quality of the couple relationship (Aarts et al., 2011; Donarelli et al., 2016; Maroufizadeh, Ghaheri, Amini, & Omani Samani, 2017; Sexty et al., 2018). Donarelli and colleagues (2016) studied the FertiQoL Core in an Italian sample of 301 females and 288 males and found that a four-factor solution had a good fit to the original Core-FertiQoL model (Boivin et al 2011) and that the reliability of subscales was at least acceptable, with Cronbach alphas ranging from 0.65 to 0.84. The focus of Donarelli and colleagues (2016) cross-sectional study was on the FertiQoL Relational Subscale and they showed that patients with higher

scores reported also higher levels of couple commitment, dyadic adjustment, and marital satisfaction, as well as low levels of sexual concerns.

Other studies have reported that some sociodemographic and medical factors affect the FertiQoL measures. To illustrate, older people were more likely to report better QoL (Huppelschoten et al., 2013; Porat-Katz, Paltiel, Kahane, & Eldar-Geva, 2016), and a higher educational level was associated with better adjustment to fertility problems (Huppelschoten et al., 2013; Karabulut, Özkan, & Oğuz, 2013; Maroufizadeh et al., 2017; Porat-Katz et al., 2016). Moreover, patients with a shorter infertility history (Karabulut et al., 2013) or without previous experience of fertility treatments (Huppelschoten et al., 2013; Keramat et al., 2014) were more likely to report better QoL. Regarding the causes of infertility, recent studies measuring QoL through the FertiQoL have reported lower Mind-Body QoL (Keramat et al., 2014; Sexty et al., 2018) and Emotional QoL (Heredia et al., 2013) scores when the perceived cause of infertility was attributed to the combined factor. Similarly, Maroufizadeh and colleagues (2017) found that Core FertiQoL scores were lower among women who were told that the reasons for infertility were either unknown or due to mixed female / malefactors. Apart from the obvious effects of a negative outcome, it is also known that, waiting for an outcome phase affects negatively the emotional state and the QoL of ART patients. However, little is known about the possible effects of the ART stages of treatment. In a longitudinal study, Agostini and colleagues (2017) analysed the SF-36 completed by 85 women at the beginning of the ovarian stimulation, before oocyte retrieval, and around 14 days after the embryo transfer, and reported that QoL decreased throughout the treatment, and that before knowing the treatment outcome mental QoL was lower compared both to the beginning of the stimulation and to the oocyte retrieval phases. In a sample of 89 women undergoing their first treatment, Massarotti and colleagues (2019), found higher Social and Mind-Body scores of the Core FertiQoL during controlled ovarian stimulation when compared to scores during the first visit at the centre.

The main aim of the present cross-sectional study was to validate the psychometric properties of both the Core and the Treatment scales of the Italian FertiQoL version in a sample of Italian women dealing with a fertility problem in different centres. The second aim was to explore the associations between the different dimensions of fertility-related quality of life (FertiQoL subscales) and ART treatment phases of women experiencing infertility. In order to control for confounding effects due to different sociodemographic and medical characteristics of the patients, we also considered in the analysis their age, educational level, clinic centre, and number of cycles completed.

Method

Study design

This study was nested within a broader cross-sectional research project on Italian couples who rely on medical assisted reproduction techniques to achieve parenthood. Data collected from 355 women attending four centres for medically assisted reproduction in different Italian cities (Turin, Cattolica, Rome and Catania) have been analysed. Data were provided by women waiting for medical consultation or a visit at the ART centres, who were informed about the study aims and asked to fill out anonymously a brief questionnaire package.

The first part of the self-reported questionnaire set included questions regarding the sociodemographic and clinical characteristics, namely patients' age (in years), citizenship, place of birth, educational level (0= None, 1=Elementary School, 2= Middle School, 3= High School; 4=University Degree), the number of treatment cycles completed, the infertility perceived causes (0= None, 1= Female factor, 2=Male factor, 3=Mixed factor) and the phase of ART treatment the woman was undergoing when she answered the questionnaire (1=Diagnostic phase, 2= Stimulation phase and 3=Transfer phase). Regarding the latter, patients completed the FertiQoL either while waiting to be visited either at their first access to the centre (Diagnostic), during ovarian stimulation and before oocyte retrieval (Stimulation), or on the embryo transfer day (Transfer). The final section of the questionnaire included both FertiQoL modules.

Inclusion criteria were having fertility problems for at least twelve months, being over 18 years of age, and having enough knowledge of the Italian language to be able to complete the questionnaire. Both nulliparous and multiparous women were included in the study. All participants were informed about the aim of the study, how their data would be managed, their right to quit the research at any time without consequences and had to sign an informed consent. Each woman participated on a volunteer basis and did not receive any compensation. All data remained anonymous. The Department of Psychology, "Sapienza" University, and the participating centres approved the study.

Sample

Data from 355 women experiencing fertility problems were collected. During the preliminary analysis, 32 questionnaires were excluded due to missing data in the FertiQoL questionnaire. The final sample was composed of 323 questionnaires. Of the final sample, 22.6% of the questionnaires were collected in an ART centre in Turin, 26.0% in Cattolica, 24.5% in Rome, and 26.9% in Catania. Participants' characteristics across the four ART centres are presented in Table 1.

The mean patients' age was 37.18, ranging between 23 and 46 years of age. Regarding educational

level, 7.7% of the patients had a middle school education, 35.0% completed high school, and 52.9% had a university degree. The number of previous treatment cycles ranged from 0 to 10 (M= 1.96; SD= 1.89). Regarding the three stages of treatment, 41 women were in Diagnostic (12.7%), 112 in Stimulation (34.7%), and 150 in Transfer (46.4%).

PLEASE INSERT TABLE 1 APPROXIMATELY HERE

Table 1. Sample characteristics across the four centres.

FertiQoL

The FertiQoL questionnaire used (http://sites.cardiff.ac.uk/fertiqol/files/2015/02/fertiqol-Italian.pdf) comprises two modules: the Core-FertiQoL module and the Treatment-module. The Core module contains 24 items organized into four subscales, and the Treatment module contains 10 items organized into two subscales as well as a Global scale. For all items, participants are asked to rate how frequently or how strongly the statements reflect their feelings and thoughts. The Likert-type item format consists of 5 choices (0–4). Higher scores indicate a better fertility-specific QoL.

The Core-FertiQoL module. Items are specific to infertility-related QoL personal aspects and cover four domains derived from the item-generation phase and are developed through exploratory factor analyses. Six items examine the impact of fertility problems in the Emotional domain (resentment, sadness, depression; e.g. "*Do your fertility problems cause feelings of jealousy and resentment?*"). Six items in the Mind-Body subscale consider the influence of infertility on physical health (e.g. fatigue, pain), cognition and behaviour (e.g. poor concentration, disrupted daily activities, delayed life plans; e.g. "*Are your attention and concentration impaired by thoughts of infertility?*"). To evaluate the interpersonal QoL items investigate the impact of fertility problems in the Relational domain (6 items; e.g. "*Are you satisfied with your sexual relationship even though you have fertility problems?*") and Social domain (6 items; e.g. "*Are you satisfied with the support you receive from friends with regard to your fertility problems?*"). The Relational subscale measures the extent to which components of the marital relationship or partnership (e.g. sexuality, communication, and commitment) have been affected by fertility problems. The Social subscale quantifies the impact of sterility on social interactions (e.g. social inclusion, expectations, stigma, and support).

The FertiQoL Treatment module. A unique aspect of FertiQoL, compared with other QoL measures, is the treatment module based on 10 items. It can be administered to evaluate satisfaction with the treatment environment and the treatment impact on the QoL of patients currently being treated for infertility. The module measures satisfaction with the Quality of the Treatment Environment (6 items: interactions with staff, quality of information; e.g. "*Are you satisfied with the quality of*

services available to you to address your emotional needs?"), and Treatment Tolerability (4 items: effects on mood, disruptions of daily life; e.g. "*Does infertility treatment negatively affect your mood?*"). These subscales can be used to assess the advantages of new treatments/medications, to monitor the quality of services and to optimize the patients' treatment experiences. Research has shown that the perceived quality of treatment and its tolerability, assessed with other instruments, are predictors of treatment satisfaction (Dancet et al., 2010) and willingness to persevere (Olivius et al., 2004).

Scaled scores for the subscales are calculated by adding all the items scores, multiplying the sum by 25, and dividing the product by the total number of items. Module scores (Core and Treatment) and a Global scale (Total FertiQoL) are calculated using the same procedure.

Statistical analysis

In order to test the hierarchical structure of the scale proposed by Boivin and colleagues (2011), confirmatory factor analyses (CFA) of the Italian 34-item version of the FertiQoL were conducted using AMOS software (IBM, Crawfordville, FL, USA). The hierarchical structure presumes that each item measures only one first-order latent factor corresponding to each subscale (i.e. Emotional, Mind-Body, Relational, Social, Environment, and Tolerability), that in turn loads only one of the two-second order factors (i.e. Core QoL and Treatment-related QoL). The factorial structure tested posits that the first-order factors corresponding to the Emotional, Mind-Body, Relational, and Social subscales load on the QoL Core second-order factor, while the latent dimensions corresponding to the Environment and Tolerability subscales load onto the Treatment-related QoL factor.

Model parameters were estimated using the Maximum Likelihood (ML) method, and the quality of the measurement model was examined through the fit indices estimates of Comparative Fit Index (CFI), and Root Mean Square Error of Approximation (RMSEA) (Hu & Bentler, 1999). Model fit was also evaluated by calculating the χ^2/df ratio of the model, which tends to correct for the typical sensitivity to sample size of this type of analysis. According to literature, a model is considered a good fit if the x2/df is <3; the comparative fit index (CFI) are all >0.90; and the root mean square error of approximation (RMSEA) values are approximately 0.06 (Hu & Bentler, 1999). Significance for all analyses was set at p <0.05.

Subsequently, we analysed the reliability of each subscale and of the entire questionnaire in terms of internal consistency (i.e. Cronbach's Alpha). Differences in patients' characteristics (e.g. age, educational level and number of previous treatment cycles) between the three phases of treatment were tested with one-way ANOVA and independent chi-square tests. These analyses were performed using the Statistical Package for the Social Sciences (version 25.0 for Windows, SPSS

Inc., Chicago, IL, USA).

Finally, to address the second aim of the study, a structural equation modelling (SEM) approach was used to test a single model hypothesizing that treatment phase may have a direct effect on FertiQoL dimensions, namely on the Emotional, Mind-body, Relational, Social, Tolerability and Environment dimensions (see Figure 1). Furthermore, in order to control the possible effects of background and treatment-related variables on FertiQoL dimensions, the model also included the direct effects of patients' age, educational level, clinic centre and number of cycles completed. Within the model, the FertiQoL dimensions (i.e. Emotional, Mind-body, Relational, Social, Tolerability and Environment) were included as separate latent constructs considering the corresponding subscale items as measurement indicators. The treatment phase was considered as a unique observed variable with three levels (1= Diagnostic Phase, 2=Stimulation Phase, 3=Transfer Phase), while the educational level was an observed variable with four levels (1=Elementary School, 2= Middle School, 3= High School; 4=University Degree). Age and number of cycles completed by the patients were instead considered in the model as continuous observed variables. Finally, the possible effects of patients' clinical centre (i.e. Turin, Cattolica, Rome and Catania) were controlled by including in the model three dummy variables representing the Turin (1 Vs. 0), Cattolica (1 Vs. 0) and Catania (1 Vs. 0) centres, while the Rome centre was treated in the analysis as a reference category.

As for CFA, the SEM analysis was conducted using the AMOS software (IBM, Crawfordville, FL, USA) and the Maximum Likelihood (ML) method was used to estimate model parameters.

PLEASE INSERT FIGURE 1 APPROXIMATELY HERE

Figure 1. Hypothesized model

Results

Confirmatory factorial analysis

The CFA results revealed adequate fit indices for the tested hierarchical factor model (chi-square /df = 1.989; CFI = 0.88; RMSEA = 0.055). Table 2 shows the first-order factor loadings for each of the Core FertiQoL and Treatment-related QoL domains. Figure 2 shows the second-order factor loadings and the latent correlation between the two second-order factors (i.e. "Core" and "Treatment") of the QoL. Overall, both the first and second-order factor loadings were statistically significant ($p < 0.001$) and were mostly around or above 0.30, which is the value suggested as a cut-off for accepting a factor loading (Tabachnick & Fidell, 2007).

PLEASE INSERT TABLE 2 AND FIGURE 2 APPROXIMATELY HERE

8

Table 2. Factor loadings on FertiQoL.

Figure 2. Fertility Quality of Life second-order factors. Numbers next to the arrows represent standardized factor loadings and correlations between factors.

Internal consistency

Table 3 shows the values of Cronbach's alpha after deletion of two items (Q4: "*Do you feel able to cope with your fertility problems?*" and T2: "*Are the fertility medical services you would like available to you*?"), which lowered the reliability of the subscales they belonged to (Emotional and Environment, respectively). Overall, all the FertiQoL scales have good or acceptable internal consistency with values ranging from 0.91 to 0.70 (see Table 3).

PLEASE INSERT TABLE 3 APPROXIMATELY HERE

Table 3. Reliability coefficients of the FertiQoL subscales.

Effects of sociodemographic characteristics on Treatment Stage

Regarding the stages of treatment (Diagnosis, Stimulation, Transfer), a chi-square test revealed an association with the number of previous treatment cycles (χ^2 (6, 285) = 16.565, p= 0.011), although no significant differences were found for the educational level (χ^2 (4, 297) = 4.703, p= 0.319) and age (F (21, 300) = 0.695, *p*=0.84).-

Test of the model relations

The SEM results revealed acceptable fit indices for the tested model (chi-squared /df = 2.329; CFI = 0.79; RMSEA = 0.06). Figure 3 presents the paths between the latent variables.

With respect to the paths between the variables considered, the results of the SEM analysis showed that, in women experiencing infertility problems, the ART treatment phase was positively associated with fertility-related QoL scores in the Relational (β= 0.14, p<0.05) and in the Tolerability (β= =0.17, p<0.05) subscales, after controlling for age, educational level ART centre, and number of cycles completed.

Age and number of cycles completed showed a significant effect on the Emotional, Mind-Body and Social subscales, while educational level was only negatively associated with the Tolerability subscale.

PLEASE INSERT FIGURE 3 APPROXIMATELY HERE

Figure 3. Results and latent effects from SEM analysis regarding the tested model.

Discussion

Several studies in reproductive medicine have highlighted how important it is to assess the QoL related to infertility and to its treatment through valid and reliable measures (Boivin et al., 2011; Gameiro et al., 2015). QoL assessment may provide important information for the medical staff and for the patients themselves on the challenges and burden experienced when dealing with fertility problem so that patients' outcomes can be improved by providing psychological support to those who have low QoL scores. From this perspective, the present cross-sectional study evaluated the psychometric characteristics of all the scales of both modules of the FertiQoL Italian version in a sample of women experiencing fertility treatments in four Italian ART centres.

Findings confirm that FertiQoL in Italian is a reliable and valid questionnaire for assessing the QoL of women undergoing infertility treatment in Italy. Consistently with the original model (Boivin et al. 2011), the results supported the construct validity and the reliability of the FertiQoL scales. The CFA indicates that the FertiQoL hypothesized six-factor-structure model provides a good fit with the observed data, in accordance with previous studies (Asazawa et al., 2018; Boivin et al., 2011; Melo, Gameiro, Canavarro, & Boivin, 2012). However, three items of the Italian Core FertiQoL (Q4; Q5; Q14) had low factor loadings in their latent constructs, which is similar to findings by Sexty and colleagues (2018). Our findings for the FertQoL Core module are consistent with the four-factor model demonstrated by Donarelli and colleagues (2016) in infertile couples attending one Italian ART centre; furthermore, they indicate that this is true also when considering the FertiQoL Treatment module subscales.

The reliability of the scores of the Italian version of FertiQoL, assessed through their internal consistency, was good or at least acceptable, and excellent for the Global score, as indicated by a Cronbach's α of 0.91, while the internal consistency of the Relational subscale was relatively low (α = 0.70). Other studies have also reported that the internal consistency of the FertiQoL-Relational subscale is lower than the other Core subscales: the Cronbach's α of the Relational subscale was 0.72 both for the Dutch (Aarts et al., 2011) and the Portuguese version (Melo et al., 2012), and 0.65 for the Italian version (Donarelli et al., 2016). For all other FertiQoL subscales, Cronbach's Alphas values confirmed a good or acceptable internal consistency, especially when items Q4 (in the Emotional subscale) and T2 (in the Environment subscale) are removed. In line with previous results with the Italian version of the FertiQoL (Donarelli et al., 2016), it seems that the exclusion or modification of items Q4, T2 and Q14 may help to improve the internal consistency of the scale.

Regarding our second aim, this study tested a model hypothesizing that the ART treatment phases may have direct effects on different dimensions of fertility-related QoL, controlling for the possible

confounding effects of age, educational level, clinic centre, and number of cycles completed. First, age effects were found on the Emotional, Mind-body and Social FertiQoL subscales. In particular, older age in our sample was associated with higher Emotional, Mind-Body and Social QoL. Other studies have found that younger age is associated to lower QoL in other scales as well (Aarts et al., 2011; Chachamovich, Chachamovich, Zachia, Knauth, & Passos, 2007; Fekkes, 2003; Huppelschoten et al., 2013).One study found no significant effect (Maroufizadeh et al, 2017). It is important to note that the sample considered in our study is relatively older (mean age of 37.18) than that in other studies. Nonetheless, the mean age of our sample is in line with the recent data by the Italian National Institute of Health, which reported that the average age of women who start ART treatments is 36.8 years, and that there is a constantly increasing percentage of women aged 40 and over who turn to ART treatment (Istituto Superiore di Sanità, 2018).

Despite previous studies in women experiencing infertility problems that have reported that higher educational levels were associated with higher QoL and with better psychological health conditions (Chachamovich et al., 2010; Maroufizadeh et al., 2017; Zurlo, Cattaneo Della Volta, & Vallone, 2018), in our data there was only a significant negative effect of educational level on the Tolerability Scale. This finding may be explained by the characteristics of our sample that was characterized by high educational levels, with more than 87% of the participants having a university degree or a high school degree.

Moreover, the number of treatment cycles effects on the Emotional, Mind-body and Social subscales, with patients with more cycles reporting lower levels of QoL. These findings are in line with previous results, which demonstrated that patients without any experience of previous fertility treatments are more likely to report better QoL (Huppelschoten et al., 2013; Keramat et al., 2014). Controlling for the aforementioned sociodemographic and clinical variables, the results of the present study show that the Relational subscale and the Tolerability subscales are sensitive to the effects of the stage of treatment in which the questionnaire is completed. According to our data, women in the "transfer" stage, when compared to those who were at the centre for the "stimulation" or for the "diagnosis" phases of treatment, experience higher levels of satisfaction regarding their relationship with their partner, as well as higher levels of treatment satisfaction and a lower impact on their QoL due to the consequences of treatment. So far most studies have interviewed participants in the initial phase of treatment (e.g. Karabulut et al., 2013; Maroufizadeh et al., 2017; Sexty et al., 2018), and to our knowledge only a few studies have considered QoL at different treatment stages (Agostini et al., 2017; Massarotti et al., 2019). Massarotti and colleagues (2019), in a sample of women without previous treatment cycles, reported higher Social and Mind-Body scores of the Core FertiQoL during controlled ovarian stimulation (before egg retrieval) when

compared with scores before the treatment (i.e. during the first access to the centre). Agostini and colleagues (2017) assessed QoL through the SF-36, at the beginning of the ovarian stimulation, before oocyte retrieval, and around 14 days after the embryo transfer. The authors reported that the women's scores for each SF36 QoL indicator decreased throughout the ART treatment, and in the phase preceding the knowledge of the treatment outcome there was a decrease of mental QoL compared both to the beginning of the ovarian stimulation and to the oocyte retrieval phase. The phases considered in our study do not include the waiting for the outcome phase and we used different QoL measures.

Our results suggest that when at the centre for the embryo transfer, women experience higher tolerability when compared to the moments of stimulation and diagnosis. Indeed, there are different treatment phases where patients may be more vulnerable to experience physical and emotional burden (e.g. Gameiro et al., 2015), and according to our results, this may be true also for the "stimulation" phase, at least when compared to the embryo transfer. This suggests that assessing both treatment-related environmental and psychophysical aspects also within the diagnosis and stimulation phase may lead to improved patient-centred care, better experiences regarding the care received by patients and subsequently to a lower risk of dropping out. For instance, in the stimulation phase, psychological interventions may be focused on coping and on finding emotional regulation strategies to deal with possible side effects and inconveniences of the treatment, as well as on improving communication between the couple and to strengthen the partnership.

The present study has some relevant limitations that need to be acknowledged. First, the cross-sectional design must be considered, which means that any conclusions about the correlations found and the instruments' validity (e.g. stability) should be taken with caution. Second, the convergent validity or the predictive value of the FertiQoL scales were not assessed. Future longitudinal studies are needed to ascertain the concurrent and predictive validity of the scales, and it is necessary to examine the correlations of Italian FertiQoL when compared to other standardized scales measuring similar psychological constructs of the fertility-related QoL. Third, although data were collected in four centres across the country (North, Centre and South) in order to have a representative sample that reflects the Italian infertile women population, the sample of the present study was not equally distributed for the stage of treatment across the clinical centres, which limits the interpretability of the differences across centres. Interestingly, the centre with most patients in the transfer stage (Turin) was also the centre where the Tolerability and treatment scores were higher. Fourth, although the FertiQoL questionnaire is an instrument designed to assess the QoL among both men and women, our sample included only women. Thus, future studies regarding FertiQoL should consider also samples that include both men and couples to better represent the Italian population

experiencing infertility. Finally, although according to Aarts and colleagues (2011) patients with a high QoL had lower levels of anxiety and depression, which influence the patients' experiences with fertility care (Aarts et al., 2012), we did not use measures of affective state. Future longitudinal studies should use affect measures (e.g. the Hospital Anxiety and Depression Scale) and explore the role of possible confounds (e.g. marital satisfaction, depressive symptoms) when assessing the QoL, as well as assess the possible variations of FertiQoL subscales across treatment phases. Moreover, the present study considered neither the waiting for outcome phase nor the period after a successful or unsuccessful outcome. Future longitudinal studies should consider the assessment of patients' QoL across their treatment pathway (before, during and after treatment).

In general, the assessment of QoL and of Treatment satisfaction with the FertiQoL should be a standard routine in ART centres and could be complemented by targeting psychological interventions, which may reduce the burden and improve patients' QoL by taking into account the different treatment stage experiences. In line with this, Domar and colleagues (2015) reported that a cognitive coping and relaxation intervention significantly increases both positive reappraisal coping and positive affect on what concerns fertility treatment and quality of life. Furthermore, several studies have found that interventions focused on the acquisition of specific coping skills (Boivin, 2003) and broader support interventions (e.g. cognitive behavioural therapy and mind/body interventions) could benefit fertility patients in reducing psychological distress (Chow, Cheung, & Cheung, 2016; de Liz & Strauss, 2005; Frederiksen, Farver-Vestergaard, Skovgard, Ingerslev, & Zachariae, 2015; Luk & Loke, 2016). However, past interventions have mostly targeted patients after a cycle or when treatment ended; thus, future intervention studies may consider specific treatment stages. For example, interventions may happen either in the stimulation phase when patients are dealing with possible treatment side effects and inconveniences, in the waiting phase when the distress of uncertainty is high or around the oocyte retrieval period when patients may experience more anxiety and pain during retrieval.

References

Aarts, J. W. M., Huppelschoten, A. G., Van Empel, I. W. H., Boivin, J., Verhaak, C. M., Kremer, J. A. M., & Nelen, W. L. (2012). How patient-centred care relates to patients quality of life and distress: A study in 427 women experiencing infertility. *Human Reproduction*, *27*(2), 488–495. https://doi.org/10.1093/humrep/der386

Aarts, J. W. M., Van Empel, I. W. H., Boivin, J., Nelen, W. L., Kremer, J. A. M., & Verhaak, C. M. (2011). Relationship between quality of life and distress in infertility: A validation study of the Dutch FertiQoL. *Human Reproduction*, *26*(5), 1112–1118. https://doi.org/10.1093/humrep/der051

Agostini, F., Monti, F., Andrei, F., Paterlini, M., Palomba, S., & La Sala, G. B. (2017). Assisted reproductive technology treatments and quality of life: a longitudinal study among subfertile women and men. *Journal of Assisted Reproduction and Genetics*, *34*(10), 1307–1315. https://doi.org/10.1007/s10815-017-1000-9

Asazawa, K., Jitsuzaki, M., Mori, A., Ichikawa, T., Shinozaki, K., Yoshida, A., … Kamiyama, H. (2018). Validity and Reliability of the Japanese Version of the Fertility Quality of Life (FertiQoL) Tool for Couples Undergoing Fertility Treatment. *Open Journal of Nursing*, *08*(09), 616–628. https://doi.org/10.4236/ojn.2018.89046

Boivin, J. (2003). A review of psychosocial interventions in infertility. *Social Science & Medicine*, *57*(12), 2325–2341. https://doi.org/10.1016/S0277-9536(03)00138-2

Boivin, J., & Schmidt, L. (2005). Infertility-related stress in men and women predicts treatment outcome 1 year later. *Fertility and Sterility*, *83*(6), 1745–1752. https://doi.org/10.1016/j.fertnstert.2004.12.039

Boivin, J., Takefman, J., & Braverman, A. (2011). The fertility quality of life (FertiQoL) tool: Development and general psychometric properties. *Human Reproduction*, *26*(8), 2084–2091. https://doi.org/10.1093/humrep/der171

Chachamovich, J. R., Chachamovich, E., Ezer, H., Fleck, M. P., Knauth, D., & Passos, E. P. (2010). Investigating quality of life and health-related quality of life in infertility: A systematic review. *Journal of Psychosomatic Obstetrics and Gynecology*, *31*(2), 101–110. https://doi.org/10.3109/0167482X.2010.481337

Chachamovich, J. R., Chachamovich, E., Zachia, S., Knauth, D., & Passos, E. P. (2007). What

variables predict generic and health-related quality of life in a sample of Brazilian women experiencing infertility? *Human Reproduction*, *22*(7), 1946–1952. https://doi.org/10.1093/humrep/dem080

Chow, K.-M., Cheung, M.-C., & Cheung, I. K. (2016). Psychosocial interventions for infertile couples: a critical review. *Journal of Clinical Nursing*, *25*(15–16), 2101–2113. https://doi.org/10.1111/jocn.13361

Dancet, E. A. F., Nelen, W. L. D. M., Sermeus, W., de Leeuw, L., Kremer, J. A. M., & D'Hooghe, T. M. (2010). The patients' perspective on fertility care: A systematic review. *Human Reproduction Update*, *16*(5), 467–487. https://doi.org/10.1093/humupd/dmq004

de Liz, T. M., & Strauss, B. (2005). Differential efficacy of group and individual/couple psychotherapy with infertile patients. *Human Reproduction*, *20*(5), 1324–1332. https://doi.org/10.1093/humrep/deh743

Domar, A. D., Gross, J., Rooney, K., & Boivin, J. (2015). Exploratory randomized trial on the effect of a brief psychological intervention on emotions, quality of life, discontinuation, and pregnancy rates in in vitro fertilization patients. *Fertility and Sterility*, *104*(2), 440-451.e7. https://doi.org/10.1016/j.fertnstert.2015.05.009

Donarelli, Z., Lo Coco, G., Gullo, S., Salerno, L., Marino, A., Sammartano, F., & Allegra, A. (2016). The fertility quality of life questionnaire (FertiQoL) relational subscale: Psychometric properties and discriminant validity across gender. *Human Reproduction*, *31*(9), 2061–2071. https://doi.org/10.1093/humrep/dew168

Fekkes, M. (2003). Health-related quality of life in relation to gender and age in couples planning IVF treatment. *Human Reproduction*, *18*(7), 1536–1543. https://doi.org/10.1093/humrep/deg276

Frederiksen, Y., Farver-Vestergaard, I., Skovgard, N. G., Ingerslev, H. J., & Zachariae, R. (2015). Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: a systematic review and meta-analysis. *BMJ Open*, *5*(1), e006592–e006592. https://doi.org/10.1136/bmjopen-2014-006592

Gameiro, S., Boivin, J., Dancet, E., de Klerk, C., Emery, M., Lewis-Jones, C., … Vermeulen, N. (2015). ESHRE guideline: routine psychosocial care in infertility and medically assisted reproduction—a guide for fertility staff: Figure 1. *Human Reproduction*, *30*(11), 2476–2485.

https://doi.org/10.1093/humrep/dev177

Greil, A. L. (1997). Infertility and psychological distress: a critical review of the literature. *Social Science & Medicine (1982)*, *45*(11), 1679–1704. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9428088

Greil, A. L., McQuillan, J., Lowry, M., & Shreffler, K. M. (2011). Infertility treatment and fertility-specific distress: A longitudinal analysis of a population-based sample of U.S. women. *Social Science & Medicine*, *73*(1), 87–94. https://doi.org/10.1016/j.socscimed.2011.04.023

Heredia, M., Tenías, J. M., Rocio, R., Amparo, F., Calleja, M. A., & Valenzuela, J. C. (2013). Quality of life and predictive factors in patients undergoing assisted reproduction techniques. *European Journal of Obstetrics Gynecology and Reproductive Biology*, *167*(2), 176–180. https://doi.org/10.1016/j.ejogrb.2012.12.011

Hu, L., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal*, *6*(1), 1–55. https://doi.org/10.1080/10705519909540118

Huppelschoten, A. G., Van Dongen, A. J. C. M., Verhaak, C. M., Smeenk, J. M. J., Kremer, J. A. M., & Nelen, W. L. D. M. (2013). Differences in quality of life and emotional status between infertile women and their partners. *Human Reproduction*, *28*(8), 2168–2176. https://doi.org/10.1093/humrep/det239

Istituto Superiore di Sanità, R. N. P. (2018). *Attività del Registro Nazionale Italiano della Procreazione Medicalmente Assisitita 2016*.

Karabulut, A., Özkan, S., & Oğuz, N. (2013). Predictors of fertility quality of life (FertiQoL) in infertile women: Analysis of confounding factors. *European Journal of Obstetrics Gynecology and Reproductive Biology*, *170*(1), 193–197. https://doi.org/10.1016/j.ejogrb.2013.06.029

Keramat, A., Masoomi, S. Z., Mousavi, S. A., Poorolajal, J., Shobeiri, F., & Hazavhei, S. M. M. (2014). Quality of life and its related factors in infertile couples. *Journal of Research in Health Sciences*, *14*(1), 57–63. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24402852

Luk, B. H.-K., & Loke, A. Y. (2016). A Review of Supportive Interventions Targeting Individuals or Couples Undergoing Infertility Treatment: Directions for the Development of Interventions. *Journal of Sex & Marital Therapy*, *42*(6), 515–533.

https://doi.org/10.1080/0092623X.2015.1074133

Maroufizadeh, S., Ghaheri, A., Amini, P., & Omani Samani, R. (2017). Psychometric properties of the fertility quality of life instrument in infertile Iranian women. *International Journal of Fertility and Sterility*, *10*(4), 371–379.

Massarotti, C., Gentile, G., Ferreccio, C., Scaruffi, P., Remorgida, V., & Anserini, P. (2019). Impact of infertility and infertility treatments on quality of life and levels of anxiety and depression in women undergoing in vitro fertilization. *Gynecological Endocrinology*, *0*(0), 1–5. https://doi.org/10.1080/09513590.2018.1540575

Matthiesen, S. M. S., Frederiksen, Y., Ingerslev, H. J., & Zachariae, R. (2011). Stress, distress and outcome of assisted reproductive technology (ART): a meta-analysis. *Human Reproduction*, *26*(10), 2763–2776. https://doi.org/10.1093/humrep/der246

Melo, C., Gameiro, S., Canavarro, M. C., & Boivin, J. (2012). P-396 Does the FertiQoL assess quality of life? Results from the validation of the Portuguese version of the FertiQoL. In *Human Reproduction* (Vol. 27, pp. ii268–ii273). https://doi.org/10.1093/humrep/27.s2.85

Olivius, C., Friden, B., Borg, G., & Bergh, C. (2004). Why do couples discontinue in vitro fertilization treatment? a cohort study. *Fertility and Sterility*, *81*(2), 258–261. https://doi.org/10.1016/j.fertnstert.2003.06.029

Peterson, B. D., Newton, C. R., & Rosen, K. H. (2003). Examining Congruence Between Partners' Perceived Infertility-Related Stress and Its Relationship to Marital Adjustment and Depression in Infertile Couples. *Family Process*, *42*(1), 59–70. https://doi.org/10.1111/j.1545-5300.2003.00059.x

Porat-Katz, A., Paltiel, O., Kahane, A., & Eldar-Geva, T. (2016). The effect of using complementary medicine on the infertility-specific quality of life of women undergoing in vitro fertilization. *International Journal of Gynecology & Obstetrics*, *135*(2), 163–167. https://doi.org/10.1016/j.ijgo.2016.05.011

Sexty, R. E., Griesinger, G., Kayser, J., Lallinger, M., Rösner, S., Strowitzki, T., … Wischmann, T. (2018). Psychometric characteristics of the FertiQoL questionnaire in a German sample of infertile individuals and couples. *Health and Quality of Life Outcomes*, *16*(1), 233. https://doi.org/10.1186/s12955-018-1058-9

Smeenk, J. M. J., Verhaak, C. M., Stolwijk, A. M., Kremer, J. A. M., & Braat, D. D. M. (2004). Reasons for dropout in an in vitro fertilization/intracytoplasmic sperm injection program. *Fertility and Sterility*, *81*(2), 262–268. https://doi.org/10.1016/j.fertnstert.2003.09.027

Tabachnick, B. G., & Fidell, L. S. (2007). *Using multivariate statistics* (5th ed.). New York: Pearson. https://doi.org/10.1037/022267

Verhaak, C. M., Smeenk, J. M. J., Evers, A. W. M., Kremer, J. A. M., Kraaimaat, F. W., & Braat, D. D. M. (2007). Women's emotional adjustment to IVF: a systematic review of 25 years of research. *Human Reproduction Update*, *13*(1), 27–36. https://doi.org/10.1093/humupd/dml040

Zegers-Hochschild, F., Adamson, G. D., Dyer, S., Racowsky, C., de Mouzon, J., Sokol, R., … van der Poel, S. (2017). The International Glossary on Infertility and Fertility Care, 2017. *Human Reproduction*, *32*(9), 1786–1801. https://doi.org/10.1093/humrep/dex234

Zurlo, M. C., Cattaneo Della Volta, M. F., & Vallone, F. (2018). Predictors of quality of life and psychological health in infertile couples: the moderating role of duration of infertility. *Quality of Life Research*, *27*(4), 945–954. https://doi.org/10.1007/s11136-017-1781-4

Table 1 Sample characteristics across the four clinic centres

	ART centre Turin (n=73)	ART centre Catania (n=87)	ART centre Cattolica (n=84)	ART centre Rome (n=79)
Age in years mean (SD)	37.99 (3.74)	36.72 (4.84)	36.47 (3.72)	37.60 (3.85)
Education Level % (n)				
Middle School	2.7 (2)	8.0 (7)	15.5 (13)	3.8 (3)
Higher School	47.9 (35)	39.1 (34)	32.1 (27)	21.5 (17)
University Degree	49.3 (36)	48.3 (42)	44.0 (37)	70.9 (56)
Missing	-	4.6 (4)	8.3 (7)	3.8 (3)
Treatment Stage % (n)				
Diagnostic	-	35.6(31)	6.0 (5)	6.3 (5)
Stimulation	5.5 (4)	41.4 (36)	50.0 (42)	38.0 (30)
Transfer	91.8 (67)	21.8 (19)	25.0 (21)	54.4 (43)
Missing	2.7 (2)	1.1 (1)	19.0 (16)	1.3 (1)
Infertility Causes % (n)				
Female Factor	21.9 (16)	18.5 (17)	3.6 (3)	25.3 (20)
Male Factor	16.4 (12)	18.4 (16)	3.6 (3)	20.3 (16)
Mixed Factors	5.5 (4)	2.3 (2)	1.2 (1)	6.3 (5)
Age-related	11.0 (8)	4.6 (4)	-	6.3 (5)
Unexplained	4.1 (3)	4.6 (4)	2.4 (2)	2.5 (2)
Do not know the cause	17.8 (13)	24.1 (21)	8.3 (7)	24.1 (6)
Do not answer	23.3 (17)	26.4 (23)	81.0 (68)	15.2 (12)
Treatment duration in months mean (SD)	16.43 (22.52)	16.84 (20.26)	19.07 (18.37)	19.83 (16.92)
Previous treatment cycles				
0 cycles	27.4 (20)	31.0 (27)	17.9 (15)	16.5 (13)
1 cycle	17.8 (13)	24.1 (21)	20.2 (17)	17.7 (14)
2-3 cycles	30.1 (22)	26.4 (23)	28.6 (24)	43.0 (34)
≥ 4 cycles	20.5 (15)	8.0 (7)	23.8 (20)	15.2 (12)
Missing	4.1 (3)	10.3 (9)	9.5 (8)	7.6 (6)

Figure 1. Hypothesized model
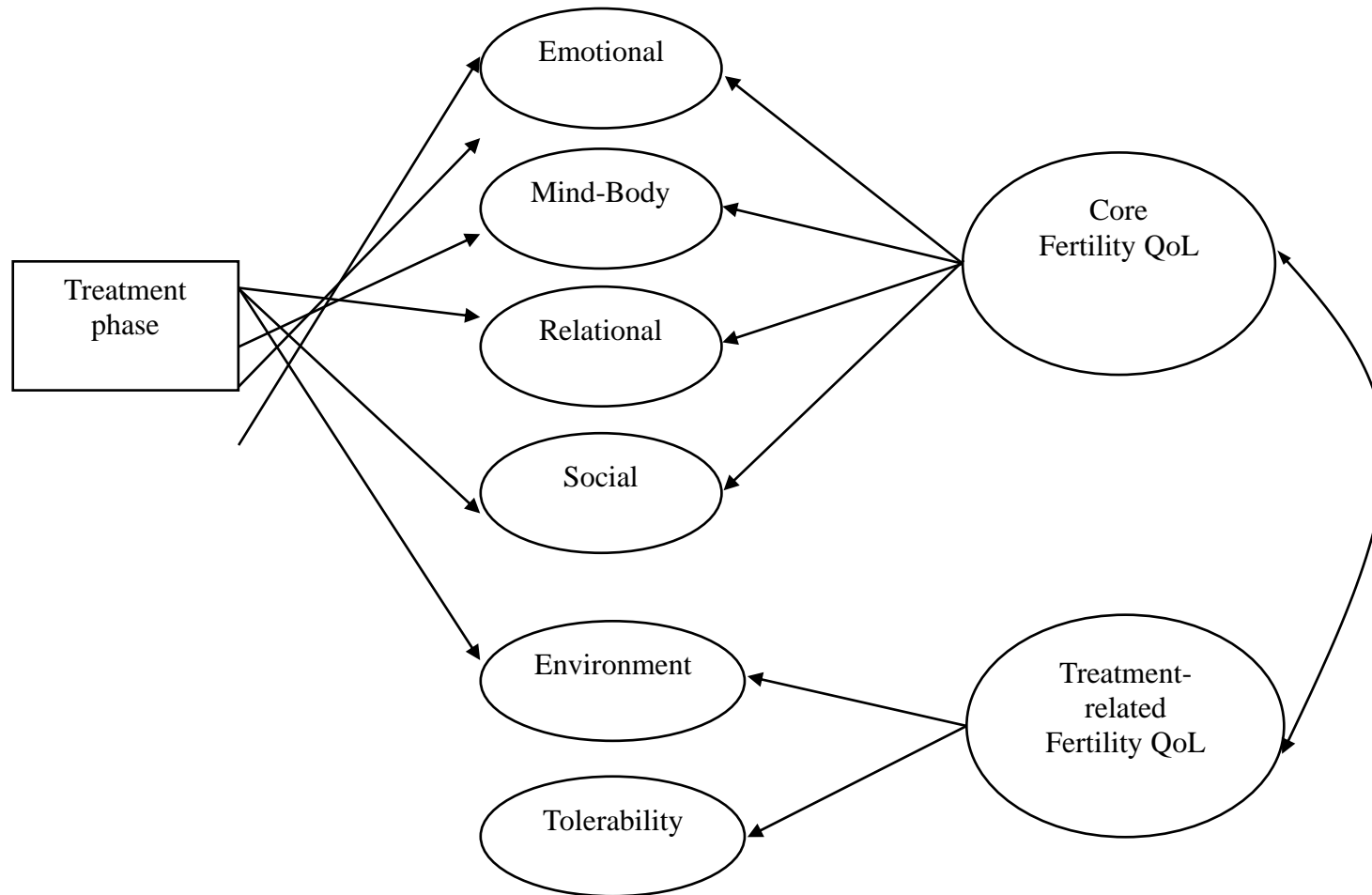
Table 2

First Order Factor loadings on FertiQoL

	First Order Factor Loadings
FertiQOL Core Subscales	
Emotional	
(Q9) Fluctuate hope / despair	0.79
(Q16) Sad / depressed	0.80
(Q8) Grief / loss	0.77
(Q23) Angry	0.75
(Q7) Jealousy and resentment	0.64
(Q4) Unable to cope	0.32
Mind-Body	
(Q3) Feel worn out	0.80
(Q18) Fatigue	0.78
(Q2) Life on hold	0.70
(Q24) Pain / discomfort	0.67
(Q12) Disrupt activities	0.62
(Q1) Concentration	0.63
Relational	
(Q19) Negative impact on the relationship	0.80
(Q20) Difficult to talk	0.70
(Q21) Content relationship	0.59
(Q6) Satisfied sexual relationship	0.43
(Q11) Affectionate	0.37
(Q15) Strengthen relationship	0.33
Social	
(Q17) Handle / pregnant others	0.80
(Q13) Shame / embarrassment	0.75
(Q10) Isolated	0.72
(Q22) Society expects	0.61
(Q5) Friend support	0.29
(Q14) Family understand	0.22
FertiQOL Treatment Subscales	
Environment	
(T7) Quality emotional services	0.74
(T10) Interaction with stuff	0.72
(T8) Quality surgery and medical treatment	0.67
(T9) Quality treatment information	0.66
(T5) Fertility staff understand us	0.57
(T2) Medical services desired available	0.38
Tolerability	
(T4) Bothered effect daily activities and works	0.71
(T6) Bothered physical effects	0.70
(T1) Treatment effects on mood	0.57
(T3) Complicated medication and procedures	0.52

Figure 2 Fertility Quality of Life second-order factors. Numbers next to the arrows represent standardized factor loadings and correlations between factors.
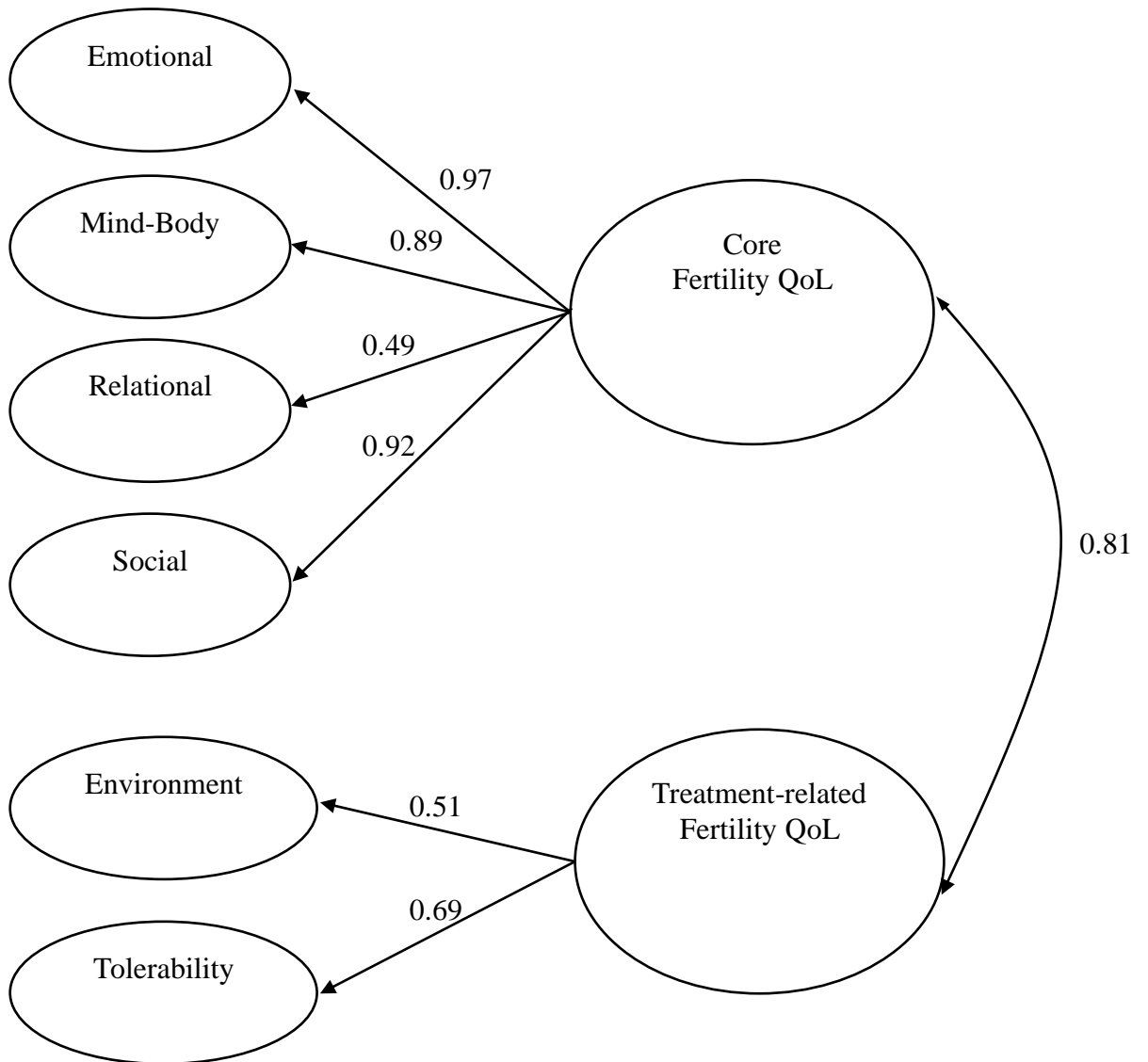
Table 3 Reliability coefficients of the FertiQoL subscales

Scale		QoL domain	N. of items	Cronbach's Alpha
Core FertiQoL		Average quality of life in all core sub-domains	23	0.90
Subscales	*Emotional*	Impact on emotions (e.g. causes sadness, resentment, grief)	5 (without Q4)	0.87
	Mind-Body	Impact on physical health (e.g. fatigue, pain), cognition (e.g. poor concentration) and behavior (e.g. disrupted daily activities)	6	0.85
	Relational	Impact on partnership (e.g. sexuality, communication and commitment)	6	0.70
	Social	Impact on social aspects (e.g. social inclusion, expectations and support)	6	0.72
Treatment FertiQoL		Average quality of life for all treatment sub-domains	9	0.78
Subscales	*Environment*	Impacts related to treatment environment (e.g. access, quality, interactions with staff)	5 (without T2)	0.81
	Tolerability	Impacts due to consequences of treatment (e.g. physical and mood effects, daily disruptions)	4	0.71
	Total FertiQoL	The average quality of life for all the scales in the Core and Treatment domains	32	0.91

Figure 3 Results and latent effects from SEM analysis regarding the tested model.
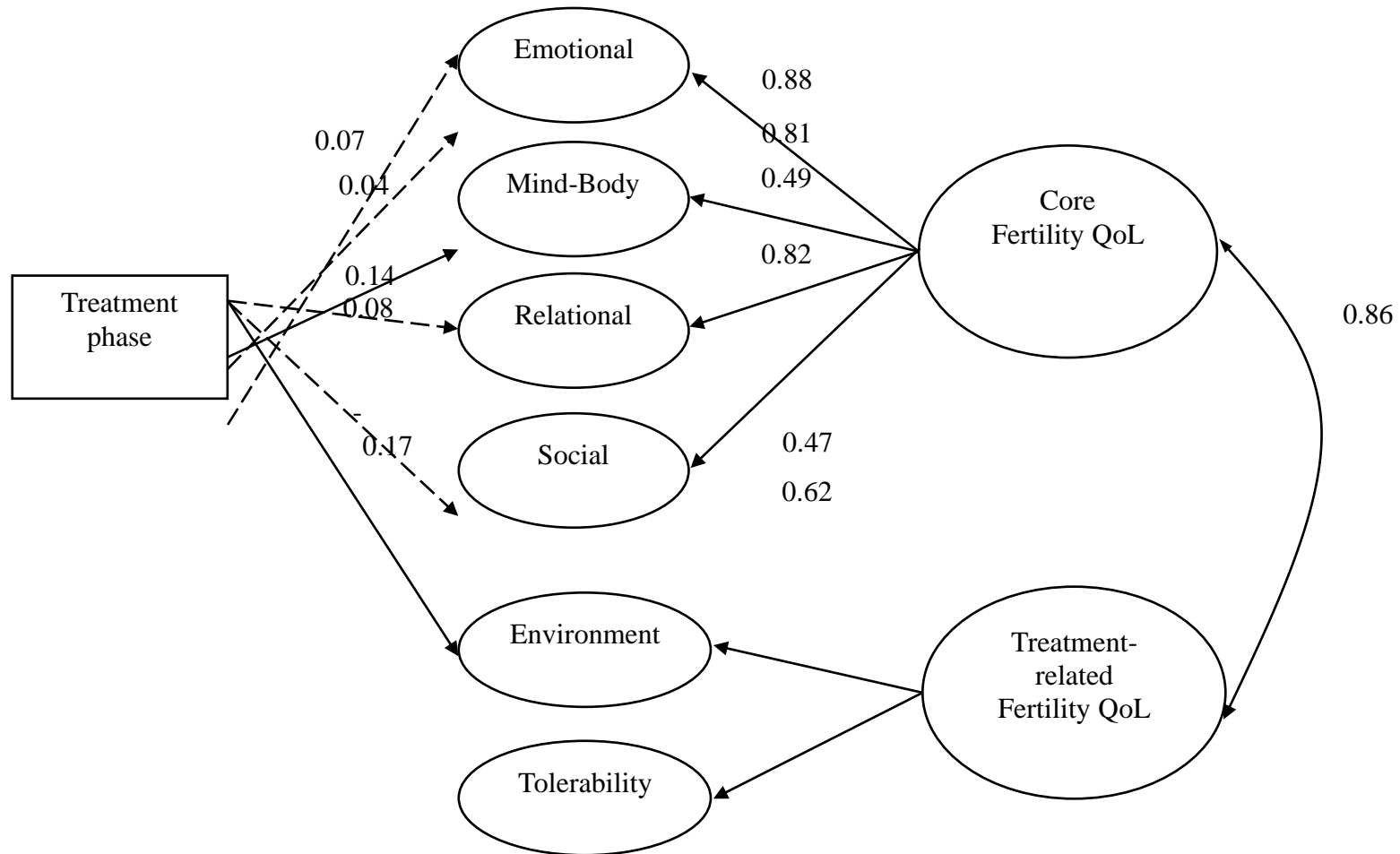
Note. Standardized path coefficients for the structural equation model estimated in the analysis controlling for age, educational level clinic centre and number of cycles completed. The effects of age, educational level clinic centre and number of cycles completed on each variable in the model figure were omitted for clarity. These paths were freely estimated analysis but not depicted in diagram:

Age → Emotional Scale (β = 0.19, *p*<0.001); Age → Mind-Body Scale (β = 0.22, *p*<.001); Age → Relational Scale (β = -0.12, *p*=0.06); Age → Social Scale (β = 0.16, *p*<0.01); Age → Environment Scale (β = -0.08, *p*=0.18); Age → Tolerability Scale (β = 0.09, *p*=0.18).

Educational Level → Emotional Scale (β = -0.08, *p*=0.14); Educational Level → Mind-Body Scale (β = -0.01, *p*=0.94); Educational Level → Relational Scale (β = 0.02, *p*=0.71); Educational Level → Social Scale (β = -0.08, *p*=0.17); Educational Level → Environment Scale (β = -0.1, *p*=0.12); Educational Level → Tolerability Scale (β = -0.17, *p*<0.05).

N. of cycles completed→ Emotional Scale (β = -0.35, *p*<.001); N. of cycles completed → Mind Body Scale (β = -0.31, *p*<.001); N. of cycles completed → Relational Scale (β = -0.1, *p*=0.14); N. of cycles completed → Social Scale (β = -0.37, *p*<.001); N. of cycles completed → Environment Scale (β = -0.10, *p*=0.11); N. of cycles completed → Tolerability Scale (β = -0.11, *p*=0.1).

Turin Centre → Emotional Scale (β = 0.04, *p*=0.52); Turin Centre → Mind-Body Scale (β = 0.10, *p*=0.07); Turin Centre → Relational Scale (β = 0.14, *p*<0.05); Turin Centre → Social Scale (β = 0.07, *p*=0.24); Turin Centre → Environment Scale (β = 0.20, *p*<0.001); Turin Centre → Tolerability Scale (β = 0.15, *p*<0.05).

Catania Centre → Emotional Scale (β = 0.04, *p*=0.45); Catania Centre → Mind-Body Scale (β = -0.01, *p*=0.87); Catania Centre → Relational Scale (β = 0.11, *p*=0.08); Catania Centre → Social Scale (β = 0.03, *p*=0.58); Catania Centre → Environment Scale (β = -0.02, *p*=0.80); Catania Centre → Tolerability Scale (β = -0.02, *p*=0.77).

Cattolica Centre → Emotional Scale (β = 0.07, *p*=0.18); Cattolica Centre → Mind-Body Scale (β = 0.15, *p*<0.05); Cattolica Centre → Relational Scale (β = 0.08, *p*=0.18); Cattolica Centre → Social Scale (β = 0.07, *p*=0.23); Cattolica Centre → Environment Scale (β = -0.003, *p*=0.96); Cattolica Centre → Tolerability Scale (β = -0.12, *p*=0.05).

Dashed lines indicate paths that were not statistically significant (p>0.05) in the SEM analysis.

*** *p* <.001; ** *p* <.01; * *p* <.005