Relationship between quality of life and distress in infertility: a validation study of the Dutch FertiQoL

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BACKGROUND: This study examined the relationship between emotional distress as measured by the Hospital Anxiety and Depression Scale (HADS) and the Fertility Quality of Life (FertiQoL) questionnaire.

METHODS: The FertiQoL and HADS were distributed to a random sample of 785 patients attending 29 Dutch clinics for medically assisted reproduction. FertiQoL was psychometrically tested for reliability. Pearson’s correlations were calculated between subscales of FertiQoL and HADS. Using an independent t-test, differences between patient subgroups were computed for both instruments. The threshold for clinically meaningful depression/anxiety on the HADS subscales was used to ascertain the critical threshold for high distress on the FertiQoL scales.

RESULTS: FertiQoL and HADS were completed by 583 patients (response 74%). Reliability of FertiQoL scales was high (reliability coefficient between 0.72 and 0.91). Significant negative correlations were found between FertiQoL subscales and HADS scores for anxiety and depression, ranging from −0.29 to −0.71. Means on FertiQoL scales and HADS scales of couples undergoing an assisted reproductive technology (ART) treatment and a non-ART treatment did not differ significantly. Patients scoring above the HADS threshold for pathology on anxiety had an average FertiQoL score of 58.8, whereas patients exceeding the HADS depression threshold had a FertiQoL total score of 51.9 (range 0–100).

CONCLUSIONS: Our study confirms the expected negative relation between quality of life as measured by FertiQoL and anxiety and depression. The data support that FertiQoL reliably measures QoL in women facing infertility. FertiQoL enables clinicians to tailor care more specifically to the patient in a comprehensive way.

Key words: quality of life / anxiety / depression / infertility / survey

Introduction

Infertility and its treatments have a significant impact on a person’s Quality of Life (QoL) (Fekkes et al., 2003; Schmidt, 2006; Verhaak et al., 2007; Chachamovich et al., 2010a). For instance, infertility is negatively associated with relational, sexual and psychosocial well-being (Drosdzol and Skrzypulec, 2008; Chachamovich et al., 2010a). Infertile patients experience, for example, more stress and tension in the relationship with their partner. Due to this impact, best practice in fertility care should involve a holistic approach and consideration of QoL should be integrated into clinical practice (Boivin et al., 2008; Chachamovich et al., 2010a). QoL comprises domains such as emotional well-being, social functioning, physical health, patient environment and personal beliefs (The WHOQOL Group, 1995; Skevington et al., 2004) and can be assessed with both generic and condition-specific instruments (Aaronson, 1988; Aignier et al., 2006; Luckett et al., 2010).

Generic measurement instruments are appreciated for their broad relevance to any population and applicability across different conditions (Wiebe et al., 2003). For example, the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) could be used to determine a patient’s emotional well-being (Verhaak et al., 2010). However, generic instruments lack specificity. Condition-specific instruments generally comprise the same domains, but include items tailored to the disease in question (Murawski and Miederhoff, 1998; Wiebe et al., 2003; Luckett et al., 2010). They are therefore believed to better reflect the consequences of that disease to a particular person and to be more responsive to changes in perceived QoL.
Relation quality of life and anxiety and depression in infertility

Materials and Methods

Recruitment of patients and inclusion/exclusion criteria

A total of 29 Dutch fertility clinics from Northern, Eastern and Western regions of the Netherlands agreed to participate in data collection. In the Netherlands, every patient visiting a Dutch hospital is assigned a code for insurance purposes according to the patient’s diagnosis and treatment. Using this diagnosis treatment combination (DBC) coding system, all patients who underwent medically assisted reproduction (MAR) in their clinic between April and June 2009 were included, varying from ART (e.g. IVF and IUI) to other forms of MAR (non-ART) [e.g. ovulation induction (OI) and IUI]. When completing the questionnaires, most women were expecting or undergoing another fertility treatment; others were awaiting the outcome of the previous fertility treatment or had recently achieved pregnancy. Those who had become pregnant during the study were excluded from the analyses, as most questions of FertiQoL are no longer applicable (e.g. ‘Do your fertility problems interfere with your day-to-day work or obligations?’) (Boivin et al., in press).

Ethical approval

The institutional ethics committee of Radboud University Medical Centre Nijmegen was reviewed and provided ethical approval for this research project to proceed. By Dutch law, ethical approval is not needed when it concerns a voluntary survey without potentially burdensome questions, which was the case in this study.

Measurement instruments

The questionnaire package comprised: (i) The Dutch version of the FertiQoL questionnaire; (ii) the Dutch version of the HADS; (iii) 10 background questions including age, duration of infertility and type of fertility treatment and (iv) blank space for comments. The questionnaire package was pre-tested among 15 infertile patients.

The FertiQoL tool was developed using mixed methods that comprised an (i) item generation phase with an expert panel (17 persons from 10 disciplines and 11 countries) and focus groups (136 patients from 6 countries) and (ii) a feasibility and acceptability phase (525 people with fertility problems from 10 countries) involving item analyses, factor analyses and reliability analysis. FertiQoL comprises two modules: the Core-FertiQoL module and the (optional) treatment-module. The latter module, which assesses current thoughts and feelings directly related to fertility treatment, was not used in the present study. The Core-FertiQoL module contains 24 items. Two items are general and 22 items specific to infertility covering four domains derived from the item-generation phase and exploratory factor analyses. The four domains are: Mind-Body (six items, e.g. ‘Do your fertility problems interfere with your day-to-day work or obligations?’), Relational (six items, e.g. ‘Have fertility problems strengthened your commitment to your partner?’), Social (six items, e.g. ‘Are you socially isolated because of fertility problems?’) and Emotional (six items, e.g. ‘Do you feel able to cope with your fertility problems?’). Psychometric analyses showed that Cronbach’s $\alpha$ is high across these domains (range 0.72–0.92) (Boivin et al., in press, www.fertiqol.org). Different response formats are used, all on a five-point Likert scale: (i) from very poor to very good (one item); (ii) from very dissatisfied to very satisfied (seven items); (iii) from completely to not at all (four items); (iv) from always to never (eight items) and (v) from an extreme amount, to not at all (six items) (see also www.fertiqol.org). The final English FertiQoL was professionally translated into Dutch from English, and checked by two local fertility experts to ensure appropriateness of wording to local customs and usage (www.fertiqol.org). The resulting questionnaire was used for the present study. A number of care providers (physicians, psychologists) and researchers went through the Dutch version of FertiQoL carefully at the beginning of this study. They could not detect items inappropriate or not applicable for the Dutch infertile population. More information on the development and translation of FertiQoL is available on the FertiQoL website www.fertiqol.org and Boivin et al., in press.

The HADS encompasses 14 items, equally subdivided into two scales measuring anxiety and depression (Zigmond and Snaith, 1983; Spinhoven et al., 1997). For instance, the item ‘Worrying thoughts go through my mind’ assesses anxiety, whereas the item ‘I have lost interest in my appearance’ evaluates the level of depression. All items needed to be answered on an ordinal four-point response scale, with tailored answer categories. In 1997, a validation study of the Dutch version of the HADS was performed in different groups of patients. The results of that study corresponded to those of the validation of the original English HADS (Spinhoven et al., 1997) and the dimensional structure and reliability of the scales appeared...
Results

Participants

In total, 594 patients filled out both the FertiQoL questionnaire and the HADS (response rate 74%). Pregnant women were excluded, resulting in 472 non-pregnant women eligible for analyses. Mean age of participants was 32.9 (SD 4.5). Of the women, 15% had a non-Dutch ethnicity and 42% had a high educational level. In 27% of cases, infertility was due to a male factor, in 26% due to a female factor, in 10% both male and female, and 37% of patients suffered from unexplained infertility. The treatment was in 51% ART, in 41% IUI and in 6% OI.

Psychometrics of FertiQoL and HADS

Cronbach’s α of HADS subscales are presented in Table I. The four factors as determined in the validation of the FertiQoL appeared to have Cronbach’s α between 0.72 and 0.91. Deleting items from one of these scales would not improve scale’s reliability. These calculations confirmed the reliable use of HADS’ and FertiQoL’s subscales. On a scale from 0 to 100, the average FertiQoL score for non-pregnant women was 70.79 (SD 13.85). Mean scores on the FertiQoL subscales and HADS subscales are also presented in Table I.

Relatedness of FertiQoL to HADS convergent validation

As shown in the last two columns of Table I, significant negative correlations were found between the FertiQoL scores and scores for anxiety and depression, ranging from −0.29 (between Relational subscale and anxiety) to −0.71 (between Mind-Body subscale and depression).

Subgroup analyses

Patients with an OI or IUI treatment had slightly higher scores on all FertiQoL scales; however, these differences were not significant. Further, ART and non-ART patients did not differ on the HADS scales.

Towards a cut-off value for the FertiQoL

The percentage of patients meeting the HADS cut-offs of eight was n = 108 (23.2%) for HADS anxiety and n = 35 (7.5%) for HADS depression. As presented in Table II, the average FertiQoL total score that corresponded to the HADS critical threshold of eight on anxiety (n = 108) was 58.8 (SD 12.7), whereas it was 51.9 (SD 13.6) for the depression cut-off (n = 35). When comparing patients with a HADS anxiety or depression score above and below eight, their FertiQoL scores on all subscales differed significantly, with the greatest significant t-value on the Mind-Body subscale (i.e. 13.3 and 9.6) and the lowest on the Relational (i.e. 5.1 and 4.6) subscale. Infertile women with a HADS anxiety/depression score above eight had significantly lower FertiQoL scores.

Effect of age on FertiQoL scoring

Univariate linear regression analysis revealed that women’s age had a positive effect on scoring on the total FertiQoL scale, Mind-Body, Emotional and Social subscale (P < 0.05), whereas it had a negative
data. To be stable across different medical settings and age groups (Spinhoven et al., 1997).

Data collection

This cross-sectional study was nested in another study, which aimed at developing and validating the Patient-Centredness Questionnaire—Infertility (van Empel et al., 2010a,b). Participation in the survey was voluntary and anonymous. Patients were sent a reminder card 3 weeks after the initial mailing. Another 2 weeks later, non-responders received a reminder with a copy of the questionnaire. Questionnaire data were entered into SPSS (version 16.0 for Windows®. SPSS Inc., Chicago, IL, USA).

Data analyses

Given the large sample size, it is assumed that sampling distribution will tend to be normal—regardless of the shape of the data that is actually collected—based on the ‘central limit theorem’ (Altman and Bland, 1995; Field, 2009). Therefore, means and standard deviations (SDs) were calculated and parametric tests were used.

To determine, whether we can reliably use the same subscales of the HADS and FertiQoL as found in the original validation studies of both measurement instruments (Zigmond and Snith, 1983; Spinhoven et al., 1997; Boivin et al., in press), we psychometrically tested these constituting factors (i.e. subscales) of the FertiQoL and HADS for internal consistency by computing a Cronbach’s α coefficient to confirm reliability of these scales. Additionally, we evaluated if deleting an item from a subscale would improve the reliability (Cronbach’s α). Furthermore, to determine inter-relatedness of scales by means of convergent validation, Pearson’s correlation coefficients (r) were calculated between total scales and subscales of both questionnaires. Total scores and subscale scores were calculated for both the FertiQoL and HADS, following each scoring method (Zigmond and Snith, 1983; Boivin et al., in press). Response categories of FertiQoL were scored according to a uniform scale to calculate mean scores: a value of 0 indicates the most negative answer and a value of 4 the most positive. Patients who filled out half or less of the items within a subscale were excluded from further analyses of that subscale. Higher scores on the scales meant better QoL and more anxiety/depression respectively. FertiQoL total and subscale scores can range from 0 to 100. A cut-off value for ‘pathology’, however, does not exist yet. Scores on both HADS subscales can range from 0 to 21. A score above eight on a HADS scale is suggestive of a psychiatric condition (Zigmond and Snith, 1983). An independent sample t-test was used to compute differences between ART-treated (i.e. IVF/ICSI) versus non-ART (i.e. IUI or OI)-treated patients for both measurement instruments. Furthermore, differences on FertiQoL scores between patients with a HADS anxiety/depression score higher than eight versus a score lower than eight were explored using a t-test. Differences were presented as t-values, reflecting the difference between both groups taking the standard error of difference into account. Finally, univariate linear regression analysis was used to explore if women’s age (independent variable) had an effect on FertiQoL scoring (FertiQoL scales as dependent variables). In all analyses, P-values < 0.05 were considered significant.

to be stable across different medical settings and age groups (Spinhoven et al., 1997).
effect on scoring on the Relational subscale ($P < 0.05$). However, age accounted for $< 4\%$ of the variability in FertiQoL scores. Based on $R^2$, 1.7\% (Relational subscale) to 3.7\% (Mind-Body subscale) of variance in FertiQoL scoring could be explained by age.

**Discussion**

Our study confirms the expected negative relationship between QoL and anxiety and depression. Infertile patients with a high QoL had lower levels of anxiety or depression, and vice versa. This negative relation is in accordance with the results of other authors (Wells et al., 1989; Bonicatto et al., 2001; Aignier et al., 2006) and other infertility studies assessing QoL for specific types of infertility (e.g. Jones et al., 2008, for polycystic ovary syndrome). This confirms the convergent validity of FertiQoL. The highest negative correlation was found between the Mind-Body subscale and HADS subscales. The Mind-Body subscale assesses effects of infertility on cognitive (e.g. attention and concentration) and somatic (e.g. feeling worn out) domains as well as disruptions to daily functioning (e.g. negative impacts on work or obligations, disturbed life plans). Importantly, all items of FertiQoL are specific to infertility (‘Are your attention and concentration impaired by thoughts of infertility’); therefore, associations either represent infertility-related decrements in QoL and their impact on emotional disorders or ways by which general depression could potentiate the negative impacts of infertility. By contrast, aspects such as sexuality and commitment to the partner (Relational domain) are less related as shown by the weak correlation. One possible explanation for the weaker correlation is due to the equivocal findings on the impact of infertility on marital satisfaction and sexuality (Coefﬁn-Driol and Giami, 2004).

Furthermore, an overlap between subscales of the FertiQoL (e.g. Mind-Body and Emotional subscale) and the anxiety/depression scales is likely due to the use (by necessity) of at least some similar items (e.g. impact on day to day activities) to achieve a comprehensively defined QoL construct as recommended by World Health Organization (Skevington et al., 2004).

This overlap, however, warrants a critical discussion of whether distress or mood and QoL are actually independent domains. Although the evaluative concept of QoL is not always consistently defined (The WHOQOL Group, 1995; Aignier et al., 2006), it involves primarily a reflection of patients’ functioning in relation to their health status in a broad sense. Anxiety and depression are, in contrast,
This study has some important strengths. Although the relatedness of a disease-specific and a generic instrument measuring QoL in infertility has been evaluated before (Jones et al., 2001; Jones et al., 2004; Schanz et al., 2005), the association between the FertiQoL and anxiety and depression had not yet been investigated. Furthermore, to our knowledge, this is the first study to report on FertiQoL after its development. Our results demonstrate the same pattern of mean scores on the different subscales as was found in the development study of FertiQoL (Boivin et al., in press; www.fertiqol.org), although QoL in our Dutch population tended to be higher. Reliability of FertiQoL scales was also high in our Dutch study population, which contributes to the external validation of the FertiQoL. Infertility appears to have more impact on negative emotions, such as jealousy and sadness, than on sexuality or commitment to the partner. Other strengths of the present study are the random, large and diverse patient sample and the response rate of 74%. Since participants received both ART and non-ART treatments, and originated from 29 different clinics, this sampling ensures representativeness for the Dutch population of women with fertility problems.

Some limitations need to be discussed. First, the study population did not include patients in the pre-treatment or diagnostic phase. However, it did include data from patients using IUI and IOL and this is valuable given that the majority of studies on QoL in infertile patients focus on an ART-treated population (Fekkes et al., 2003; Ragni et al., 2005; Rashidi et al., 2008; Chachamovich et al., 2010a). A second limitation of this study originates from the cross-sectional study design, which means that statements on causality between QoL, anxiety, depression and being infertile cannot be made. Third, the FertiQoL can assess the QoL in both women and men separately. For practical reasons, we only asked women to complete the FertiQoL questionnaire. However, several authors reported that men feel marginalized and overlooked in fertility care (Schanz et al., 2005; Malik and Coulson, 2008; Chachamovich et al., 2010b) even though the negative effect of infertility on their lives is smaller and their QoL mostly higher than in women (Fekkes et al., 2003; Schanz et al., 2005; Peterson et al., 2009; Chachamovich et al., 2010b; Klemetti et al., 2010). Therefore, it would be important to also question infertile men on QoL issues and evaluate the reliability and clinical value of using FertiQoL with infertile men. Fourth, the simultaneous validation of the Patient-Centredness Questionnaire—Infertility in the same patient group could be burdensome for participants. However, the fairly high response rate of 74% does not support this limitation. Also other research has shown that the length of a questionnaire does not keep patients from completing it (Gallagher and Fowler, 1998). Additionally, the complete questionnaire package was pre-tested among 15 infertile patients and none of them claimed to be hindered by the length of the questionnaire.

In conclusion, our data make it plausible that the Dutch version of FertiQoL, a tool that was specifically created for infertile patients, can reliably and accurately evaluate QoL in women who underwent a fertility treatment in the Netherlands. Given its properties, the disease-specific FertiQoL provides clinicians with detailed information about those domains in a patient’s life that are affected most (Murawski and Miederhoff, 1998; Wiebe et al., 2003). This way, fertility care can be tailored more specifically to the individual patient in a comprehensive and holistic way.
Authors’ roles
J.A. designed the study, developed and managed the main database, interpreted the analysis and drafted the paper. I.W. designed the study, developed the main database, analysed and interpreted the data and drafted the paper. J.B., W.N. and J.K. contributed to the interpretation of data and revised critically for important intellectual content. C.M. designed the study, interpreted the data and drafted the paper. J.A. designed the study, developed and managed the main database, interpreted the analysis and drafted the paper. I.W. designed the study, developed the main database, analysed and interpreted the data and drafted the paper.

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