The effect of infertility on mental health in infertile women and men

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Introduction

Motives behind childbearing

Childbearing has outstanding importance on cultural and individual aspects. The desire of having a child is multifactorial; its motives can be the age, marital status, cultural and economic expectations or religion affiliation as well. To sever or rank these motives is a difficult task.

Infertile women and men form a proper group for investigating motivations of becoming parents. These motivations can be hidden in healthy couples, but because of infertility, it manifests itself as unfulfilled desire [1]. Several studies compares men's motivation for fatherhood with women's motivation for motherhood among infertile couples [2]. Great proportion of these studies found that women's motivations are stronger than their partner's. A german study explored parental behavior and motives behind childbearing. [3]. When they examined only infertile patients, in line with literature, women's motives for having a child were stronger, but on the other hand, when they examined only the reproductive-aged subjects, the strength of the motives among men and women were nearly similar. An Australian study also investigated the motives for paternity among men diagnosed with infertility [4]. Less, than the half of the participants agreed with the statement that women suffer more from the burden of childlessness than men, and 10 percent of subjects thought that paternity is the proof of their masculinity.

Definition of infertility and epidemiology of childlessness in developed and developing countries

Infertility can be described as an inability to become conceived within one year despite regular unprotected intercourse [5]. Unintended childlessness is one of the biggest yet barely pronounced reproductive health problem in developed countries. Despite the fact that world's total population has almost tripled in the last seventy years, the total fertility rate has decreased during the same period [6]. The total fertility rate in a specific year is defined as the total number of children that would be born to each woman if she was to live to the end of her child-bearing years and give birth to children in alignment with the prevailing age-specific fertility rates [7]. According to the results of the 2015 Revision of World Population Prospects, Europe has the lowest fertility rate of 1.6 children per woman [8]. Approximately 186 million people are facing the problem of infertility worldwide and in Hungary 9 percentage of the population are affected by unintended childlessness [9].

The psychological effects of unintended childlessness

As it was shown earlier, there are several motives in the background of childbearing. Thus, it is clear that facing difficulties with fulfilling the desire of having a child have a serious impact on mental health of affected spouses. In the literature several studies are involved in the exploration of these psychological aspects affecting infertile couples. Those studies emphasize the importance of the psychological burden caused. In a study infertile couples were asked during the IVF treatment, and 50% of women and 15% of men reported that infertility is the heaviest crisis in their lives [10]. However, it has shown that reproductive function is sensitive to psychological changes and distress can also negatively affect the process of *in vitro* fertilization programs [11]. Therefore, it would be crucial to monitor and screen the patient's mental status during infertility treatments.

The main proportion of the literature focuses on the gender-differences of infertility-related mental health, especially focusing on women [12]. This attitude is understandable considering the psychological aspects of childlessness amongst men have been less evaluated compared to women in the past. In these studies, depression, anxiety and decreasing quality of life are mostly emphasized as the expression of mental burden [13]. Nevertheless, the psychological aspects of childlessness amongst men have been less evaluated compared to women in the past. Furthermore, these previously published studies have usually been conducted at fertility clinics after some kind of therapeutic interventions, which might be a noteworthy influencing factor to the participant's psychological state as well. In these studies, the mental burden caused by childlessness cannot be distinguished from the effects of diagnosis or the medical intervention. Besides, studies focusing to the gender differences related to infertility examine the patients as individuals and not counts with the spousal effect on the psychological reaction.

Our studies main purpose was to investigate the less examined infertility-related psychological effects amongst men. In our first study we aimed to evaluate the consequences of unintended childlessness alone on the general anxiety and depression levels of the male partner. To minimize the psychological effect of infertility diagnosis and treatments, our study was carried out amongst men who were seeking an infertility evaluation for the very first time. In our second study we used dyadic approach to measure the spousal effect on mental health in connection with unintended childlessness. Our aim was also to emphasize the importance of a screening process related to the participant's psychological state, in which every patient should

participate before infertility treatment, and to work out an alternative, reliable and effective clinical method for that.

Materials and methods

Design of the studies

In our first study we aimed to investigate the general anxiety and depression levels in men presenting for infertility evaluation for the first time before starting the infertility work-up. Heterosexual men seeking a fertility evaluation at our Andrology Unit between September 1, 2013 and March 1, 2014 were enrolled. The possible connections between depressive and anxiety symptoms, the duration of infertility, and sperm characteristics were also investigated. After the performance of physical examination, but before semen was produced for sperm analysis, sociodemographic and medical data and information on lifestyle factors and fertility history were collected via multiple self-reported questionnaires. To assess the psychological distress visual analog scale (VAS) questionnaire was used, whilst to measure the rate of depression and anxiety a valid Hungarian version of the Beck Depression Inventory (BDI) and the Spielberger State-Trait Anxiety Inventory (STAI) was acquired. Exclusion criteria were presence of any previously diagnosed psychological disorder(s). From all of our patients informed consent was obtained and the study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000, as well as the study protocol was approved by the Regional and Institutional Human Medical Biological Research Ethics Committee.

In our second study we used a cross-sectional design with a dyadic approach to investigate how the psychological state related to infertility affects the spouses. We have examined infertile couples who were attended to our Andrology Outpatient Clinic during a time period from August 2017 to April 2019. During the examination period, the psychological state was measured by multiple questionnaires, like the BDI, STAI, well-being (WHO-5 Well-Being Index - WHO-5 WBI), general mental state (Symptom Check List- 90 Revised Test - SCL-90R), nicotine dependence (Fagerstrom Test for Nicotine Dependence - FTND), and alcohol dependence (Alcohol Use Disorders Identification Test – AUDIT*)* as well. Our primary outcome measures were the values of the level of depression, anxiety, general mental-health and well-being index. Accordingly, each case as one couple had two test results on each instrument. We identified the main characteristics of the formed clusters and examined whether the responses to the WHO-5 WBI fit the spouses into the formed groups. In addition, the data

of WHO-5 WBI, as an independent variable, were not used in the calculation process of clustering. Exclusion criteria were presence of any previously diagnosed psychological disorder(s) and/ or any severe case in life history. As in our first study, patients informed consent was obtained and the study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000, as well as the study protocol was approved by the Regional and Institutional Human Medical Biological Research Ethics Committee.

Statistical analysis

In the first study statistical analyses were performed with SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk test and analyses of the Q-Q plot diagrams demonstrated that age, body mass index (BMI), VAS scores, BDI scores, sperm characteristics, and the duration of infertility were not normally distributed while the distribution of the STAI results was normal.

The correlations between the duration of infertility and the VAS, BDI, and STAI results were determined using regression analyses. In addition, the correlation between the BDI and STAI scores and sperm characteristics were also analyzed. A multivariable linear regression analysis was also controlled for age, BMI, smoking, and the number of children. Correlation coefficients (B) were calculated for both the univariate and multiple linear regression, whereas standardized coefficients (ß) were given for univariate analyses and semipartial correlations (r) for multivariable regression. To express the results in terms of the proportion of explained variance, the square of the standardized coefficient and the square of the semipartial correlation were calculated. All variables which did not follow the Gaussian distribution were transformed logarithmically (log10(xţ1)) so that they could be included in the regression model. The distributions of BDI and STAI score categories were compared with the duration of infertility categories using the chi-square trend test. The distributions of the VAS scores among the three subgroups of the duration of infertility were assessed with the analysis of variance (ANOVA) test. Statistical significance was defined at the two-sided pĽ.05 level.

In the second study, data of each couple, both male and female were ordered into the same case. Considering the fact, that the scores of WHO-5-WBI for males and WHO-5-WBI for females are independent variables in the classification process, we examined them first for normality and outliers. We experienced one outlier on the scale of WHO-5-WBI among females. Avoiding the distortion, we excluded this case (couple) from the analysis. Health related additional instruments, Fagerstrom and AUDIT results were analyzed as basic characteristic variables.

We found that WHO-5-WBI scores differed from normal distribution for both genders, therefore Logistic Regression was used in the later statistical analysis to evaluate its predictive effectiveness.

To determine the interdependence between the male and female partner's psychological involvement (e.g.: depression, anxiety, general mental health), we separated the couples into two clusters, based on BDI-male, BDI-female, STAI-State-male, STAI-State-female, STAI-Trait-female, SCL-90R-male, SCL-90R-female results. Two-Step cluster analysis was carried out consecutively, because it considered as a robust method against a lack of normal distribution and outliers. We also determined the main characteristics of the formed groups.

As previously defined, the reliability of WHO-5-WBI classification was tested with Logistic Regression on the clusters. Reaffirming the diagnostic values of WHO-5-WBI, we performed ROC-analysis and determined the effectiveness of WHO-5-WBI.

Data were analyzed using the Statistical Package for Social Sciences (SPSS 25.0.0 for Windows, SPSS Inc., http://www.spss.com).

Results

A total of 117 patients were invited to take part in our first study, but four (3.4%) patients declined to complete the questionnaire; hence, it was the results from 113 patients that were analyzed. All of them were Caucasian. The mean age of the study population was 33.3 (range: 23–54) years. Regarding to the questionnaires, the BDI was completed entirely in 110 cases (97.3%), whereas both the STAI and VAS were completed in 102 cases (90.3%). The mean results for the BDI and STAI were 2.24 (standard deviation (SD: ±3.18) and 33.74 (SD: ±8.04), respectively. No patient was registered with high BDI scores (above 19 points), indicating moderate or severe depressive symptoms. The VAS finding relating to the self-reported psychological distress of the present examination was 2.52 on average (SD: ±2.04; range: 1–8). In univariate and multivariable analyses, significant correlations emerged with low regression coefficients between the BDI scores and the duration of infertility (pĽ.042, BĽ0.207, ß2Ľ0.038 and pĽ.024, BĽ0.241, r2Ľ0.047, respectively), whereas the STAI score showed no correlation (pĽ.120, BĽ0.005, ß2Ľ0.024 and pĽ.142, BĽ0.005, r2Ľ0.022; respectively). The result for the VAS tended to be higher with the duration of childlessness (pĽ.044, BĽ0.23, ß2Ľ0.023), but the correlation became non-significant when we controlled for other factors in the multivariable analysis (pĽ.261, BĽ0.178, ß2Ľ0.013)

There were significant correlations between the STAI and VAS scores (univariate analysis: p<.001; BĽ19.270, ß2Ľ0.174 and multivariable analysis: p<.001; BĽ20.228, r2Ľ0.181) and between STAI and BDI scores (univariate analysis: p<.001, BĽ11.192, ß2Ľ0.153 and multivariable analysis: p<.001; BĽ11.532, r2Ľ0.130) (not shown in the tables). The frequency of mild symptoms of depression (BDI score: 10–18) increased significantly as the duration of infertility grew longer (groups of 0–12 months, 13–24 months and >24 months) (pĽ.006) while the incidence of an abnormal level of anxiety (STAI score >49) (pĽ.353) and self-reported psychological distress tied to the examination (VAS scores) (pĽ.086) did not differ in these three groups. No sperm variable showed a correlation with the BDI, STAI, or VAS scores.

In our second study also all the questionnaires were self-completed and 61% of the infertile couples agreed to participate in the study and complete the questionnaires. Altogether, 65 infertile couples were enrolled. Later, we excluded one outlier couple during the statistical data analysis. Accordingly, the final calculations were performed with 64 case (n=128).

The results of the questionnaires in our study population are shown in (*Table 3).* The average age of men was 37.34 years (±5.84 SD); of women 34.07 years (± 0.06 SD). Mean BDI results were 3.59 for males and 5.17 for females. Mean scores of STAI-Trait and STAI-State tests were 33.61 and 34.73 for men, 37.36 and 37.31 for women. Mean SCL-90R-GSI was 0.33 for both genders, WHO-5-WBI mean scores was similar, 9.59 for men and 9.56 for women. With regard to smoking (Fagerstrom) and alcohol consumption (AUDIT), 68.8% of men were non-smoker, 28.3% were moderate smoker, the rest of them (2.9%) reported severe nicotine dependency. Regarding the women, 75.0% were non-smoker, 25.0% were moderate smoker and no serious nicotine addict was registered. Among men in terms of alcohol consumption, 12.5% were non-drinker, 71.9% were moderate drinker, the remainders (15.6%) were facing serious alcohol problems. In parallel, 25% of women do not consume alcohol, 68.7% can be identified as moderate drinker, the remainders (6.3%) having serious alcohol problems.

Two-step Cluster Analysis generated two distinct cluster groups with highly homogenous patterns of health-related psychological characteristics. Of the 64 couples, 53.1 % (n=34) can be classified as Cluster 1: “Infertile couples with high values on mental health inventories” and 46.9 % (n=30) as Cluster 2: “Infertile couples with low values on mental health inventories”.

Cluster 1 produced higher levels on health-related and psychologically relevant questionnaires, in contrast, the couples in Cluster 2 showed lower results. According to the cluster analysis process, all variables showed a significant difference between the two clusters. In the Cluster 1, for both men and women higher average levels of anxiety were experienced on STAI-Trait (STAI-Trait Cluster 1: men=38.32; women=43.03; Cluster 2: men=28.27; women=30.93). STAI-State also showed elevated scores by each gender in Cluster 1 (STAI-State Cluster 1: men=40.44; women=43.00; Cluster 2: men=28.27; women=30.87). BDI results also suggested that members of the Cluster 1 experience inferior conditions compared to the Cluster 2 group (BDI scores, Cluster 1: men=5.97; women=7.94; Cluster 2: men=0.90; women=2.03). Specifying the mental-health condition in general (measured with SCL-90-R), we experienced higher total scores for each gender (GSI scores: men=0.45; women=0.55) in Cluster 1, compared to Cluster 2 (men=0.10; women=0.18). In addition, men in Cluster 1 displayed higher risk for alcohol dependency (AUDIT Cluster 1: $t(62)=49.505$, $p=0.021$). The age and the level of nicotine addiction showed no significant difference between the clusters.

Logistic regression analysis was performed to assess the predictive efficiency of WHO-5-WBI on the likelihood that the infertile couples would be classified into the Cluster 1 or Cluster 2. Regarding to this, we used the cluster membership as the dependent variable in the logistic regression. The model representing predictors was statistically significant ($\chi 2$ (df 2, n_{total}: 64, $n_{cluster1}$: 26, $n_{cluster:}$ 38) = 14.59, $p<0.0001$), explaining that the model was able to distinguish between infertile couple who were separated into clusters based on their results of BDI, STAI, SCL-90R *(Table 4).* The results also show that WHO-5-WBI-male and WHO-5-WBI-female, as independent predictor variables, specify the regression with a significantly negative coefficient (WHO-5-WBI-male: 0.298, $p=0.016$; WHO-5-WBI-female: 0.474, $p=0.008$). Congruent association of predicted probabilities and observed responses was 75.0%, which is further evidence of the effectiveness of the classification. Despite the fact that couples were interpreted as cases (dyads), the values of both women and men, had a reliable diagnostic model for the couple's mental state.

For further confirmation, and showing the tradeoff between sensitivity and specificity, a Receiver Operating Characteristic curve was calculated. The appropriate ROC curve was drawn in *(Figure 1)* ($AUC_{WHO-5-WBI-male}=0.797$, 95% confidence interval: 0.689-0.904, $p<0.001$; $AUC_{WHO-5-WBI-female}=0.804$, 95% confidence interval: 0.699-0.910, $p<0.001$). The ROC analysis suggests that WHO-5-WBI as a diagnostic test has separative ability to discriminate between cluster memberships.

Discussion

The motives behind childbearing are determined by several factors amongst men and women. Unfulfilling this multifactorial desire of having a child can impose serious psychological burden to the affected spouses [14].

Depression and anxiety

Relating infertility, the most frequently experienced psychological disorders amongst infertile couples are anxiety and depression, hence a significant part of the literature focuses on the presence of these symptoms [12].

Therefore, the purpose of our first study was to investigate the effect of the duration of unintended childlessness on the psychological condition of men at the start of the infertility evaluation. In this study we aimed to distinguish the consequences of unintended childlessness from the psychological effect of infertility treatments and the diagnosis itself. To measure the correlation between the duration of childlessness and the extent of distress factors was also our purpose. In our study mild depressive symptoms were found (BDI < 19 point) in 4,5% of the patients. This proportion is nearly equal with the percent of men with moderate or severe depression symptoms (4,3-5,1%) during infertility treatment in other researches [15] [16]. According to these results we can assume that depressive symptoms are increasing as a consequence of infertility treatments.

Our study also found significant correlation between the depression symptoms and the duration of childlessness amongst the examined men, showing that the main determining factor of depression was the duration of childlessness. In numbers, 23,1% of men who suffered from unintended childlessness longer than 24 months had mild depression. Similar results had another study, that enrolled 370 infertile women to investigate infertility-related depression using BDI. According to their results depression had a significant relation with cause of infertility, duration of infertility, educational level, and job of women [17]. By measuring the connection between duration of childlessness and depression symptoms another study also found correlation amongst 114 infertile men [18].

As a result of our study we did not found significant correlation between anxiety symptoms and the duration of childlessness, prior the participants started the infertility treatments. This outcome is not in the line with the literature, where almost all studies found correlation between these two factors. [12, 14, 19]. According to this it can be assumed that the

presence of anxiety symptoms is mostly linked to the infertility treatments. This presumption is proved by Zorn at al.'s study, in which they found significant correlation between IVF and the level of anxiety [20].

In our second study we examined the mental status of couples suffering from infertility. In this study we used questionnaires describing depression and anxiety symptoms also. The results revealed that infertile couples could be separated based on the scores of SCL-90-R, STAI-State and STAI-Trait and the BDI. We were able to identify two, significantly different clusters, one (Cluster 1) with relatively high and other (Cluster 2) group with relatively low scores, and corresponding to this clustered groups, a two different group with a relatively low and high level of anxiety and depression symptoms. In Cluster 1, for both men and women higher average levels of anxiety were experienced on STAI-Trait (STAI-Trait Cluster 1: men=38.32; women=43.03; Cluster 2: men=28.27; women=30.93). STAI-State also showed elevated scores for both genders in Cluster 1 (STAI-State Cluster 1: men=40.44; women=43.00; Cluster 2: men=28.27; women=30.87). BDI results also suggested that members of the Cluster 1 experienced inferior conditions compared to the Cluster 2 group (BDI scores, Cluster 1: men=5.97; women=7.94; Cluster 2: men=0.90; women=2.03).

Dyadic approach

Although it is obvious that the unintended childlessness has huge psychological burden on both members of the affected couple, decisive proportion of the literature focus on the gender differences of mental health. Nonetheless the unfulfilled desire is a common burden, the affected couple has to face together with this serious difficulty. [13].

Therefore, the aim of our second study was to examine infertile couples and how they affect to each other's psychological state. We investigated symptoms of depression, anxiety, state of well-being and general health by several instruments (BDI, STAI, SCL-90-R, WHO-5-WBI, AUDIT, FTND) in our study. A model free clustering approach was used, and the interdependence of spouses was analyzed regarding the infertility related psychological burden. In the line with the literature the trend was observed that women experienced higher levels of perceived stress and depression in general, compared to men. The results revealed that infertile couples could be separated based on the scores of SCL-90-R, STAI-State – Trait and the BDI. Using these instruments, we were able to identify two, significantly different clusters. One (Cluster 1) with relatively high and a second (Cluster 2) group with relatively low scores. Cluster 1 could be typified as one in which spouses experienced more expressed infertility

related psychological symptoms, in contrast, couples in Cluster 2 presented lower level of anxiety and depression. Male and female psychological conditions were similar within the clusters, supporting the strong interdependence between the spouses.

In terms of the dyadic approach our results are in line with the literature as well. An Italian study evaluated the prevalence and the incidence of depressive and anxious symptoms among 1000 couples undergoing assisted reproductive treatment [21]. The study found that women with anxiety or depression symptoms had more frequently anxious partners. Depressed and anxious men had also often spouses with affected mental status. A Korean study's aim was to examine the level of infertility stress, marital adjustment, depression, and quality of life in infertile couples [22]. They found significant actor-partner effects, as the wife's infertility-related stress had a negative impact on the husband's quality of life.

In addition, we found the predictive efficiency of WHO-5-WBI on the likelihood that the infertile couples would be classified into the earlier mentioned Cluster 1 or Cluster 2. The results of this one inventory was able to distinguish between infertile couple who were separated into clusters based on their results of BDI, STAI, SCL-90R. It might be used as a first line screening by general practitioners or IVF nurses, and couples with low scores can be referred to professionals for further psychological care. In a recent review, Topp and colleagues pointed out that the WHO-5-WBI is a promising tool for assessing psychological parameters of patients, including depression and anxiety [23]. According to their results the scale has adequate validity both as a screening tool for depression and as an outcome measure in clinical trials and has been applied successfully across a wide range of study fields. In another study Henkel at al. was searching for some suitable method for identify depression in primary care [24]. They found that the WHO-5-WBI, produced significantly greater sensitivity and a better negative predictive value than the other questionnaires. The World Health Organization's recommendation that every patient in primary care should participate in a screening process with the completion of WHO-5-WBI as a standard first step, done in the waiting room [25].

In our study we found that higher level of the WHO-5-WBI predicts lower scores on the scales of BDI, STAI, SCL-90-R. This result and our ROC analysis supported that WHO-5-WBI questionnaire may be a useful tool in short mental-health assessment. It had a good separative ability on general mental health. Therefore, the WHO-5-WBI was suitable for determining the two clusters and identified couples with elevated level of psychological burden with good accuracy. In case a couple is screened using WHO-5-WBI, an expert could decide further

diagnostic or therapeutic steps, and with this method, an increased diagnostic efficiency and more targeted care can be achieved.

Limitations

Undoubtedly, our study has some limitations. In the developed countries only 56,1 percent of the infertile couples search medical help, in some of the countries this proportion is under 45 percent [15]. In the developing countries the average is 51,2 percent, some countries it does not reach 30 percent. Thus, it is hard to estimate the psychological status of this hidden part of infertile population and to create a representative summary of the mental burden of unintended childlessness. In Hungary the average may be larger due to our health care system, where the access to the infertility specialist is good, even if it is an andrology or a gynecology expert. In our first study the examined men's psychological status possibly influenced by their partners', but in our second study we have corrected this limitation.

Furthermore, only 61% of invited couples took part in the second research, which may affect our conclusion. It is possible, that couples in the worst psychological conditions did not fill the questionnaires. Hopefully, using only a short test as the WHO-5-WBI may increase the willingness of couples to participate in the psychological screening. Another limitation of our study is that we have not included questionnaires examining the coping strategies of the spouses, which can be the topic of a further study.

Conclusion

In our first study unexpectedly, low levels of depressive and anxiety symptoms were found in men at the start of infertility evaluation. A significant correlation was demonstrated between the duration of infertility and the level of depressive symptoms. In contrast there was no correlation between the duration of infertility and the level of anxiety. Based on these results and the known literature, the symptoms of anxiety and the higher depression level seems to relate to the infertility treatment itself. No correlation was found between sperm characteristics and the levels of depressive or anxiety symptoms in this study. In our first research we did not pay attention to the spousal effect that we did in our second study. As we know, it was the first research, which was able to classify couples into two significantly different clusters regarding

the infertility-related psychological burden. The mental conditions of the spouses were interdependent and similar; they were assigned into the same cluster allowing us to handle them as a dyad. However, scores from BDI, STAI, and SCL-90R questionnaires characterized mostly the mental health of the couples. But the WHO-5-WBI questionnaire also was able to identify couples with significant psychological burden. These patients need professional mental support during the infertility treatment, and we believe, based on our results, that WHO-5-WBI is a convenient tool for health care providers and the patients to identify the couples at need. The part of a psychological intervention could be the education about the link between lifestyle and infertility and also to learn the adaptive coping strategies to deal with this distressful part of the infertile couple's life.

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