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Relationship between stress and reproductive difficulties (infertility)

Theses of Ph.D. dissertation

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1. INTRODUCTION

According to the World Health Organization (WHO), infertility is defined by the failure to achieve a pregnancy after unprotected sexual life for at least one year. According to international estimates, the prevalence of infertility is about 9-15%, and about half of this population seeks medical help. Approximately 10-15% of the Hungarian population of reproductive age is beset with reproductive difficulties. The decrease in the number of children may be related to the fact that women tend to delay their first pregnancy. Behind the decision on late pregnancy there may be socio-cultural factors such as wider expansion of education, individual professional and career ambitions, existential uncertainty related to labile labour market conditions, and a change in the value system of family or partnership. Undesirable childlessness is a multifactorial phenomenon that can be approached from different perspectives. The traditional biomedical interpretation of the 20th century connects infertility only to somatic reasons, explaining it as a dysfunction of the reproduction system. The oldest psychological approach of reproductive problems is rooted in the psychoanalytic concept called psychogenic model: unsuccessful pregnancy is explained by the intra-psychic problems of a woman struggling with infertility. The psychological consequence model considers negative psychological phenomena associated with fertility problems (anxiety, depression, infertility-specific distress) as a consequence of infertility. Today the most accepted approach has become the bio-psycho-social, circular approach. The circular model breaks with the linear approach of reductive system. It means that infertility increases psychosocial distress and distress-induced physiological changes (primarily through neuro-endocrine processes) have a negative influence on the success of the treatment, therefore play a vital role in maintaining the status of infertility. Focusing on the circular approach, I analysed the relationship among reproductive difficulties and psychological well-being (depression,

anxiety) and the demographic, psychological and lifestyle factors associated with female infertility.

2. OBJECTIVES

To test our hypotheses, we have designed two studies that have the following objectives and questions:

1. Analysis of socio-demographic characteristics among infertile women on Hungarian sample.
2. Comparison of psychological characteristics (anxiety and depression) between infertile and fertile women.
3. Comparison of the psychological characteristics (anxiety, depression, infertility-specific distress) between infertile women undergoing assisted reproduction treatment and their counterparts without ART history.
4. Investigate the socio-demographic, psychological and lifestyle factors behind the anxiety and depressive symptoms of infertile women.
5. Investigate the background factors of general sources of stress related to depressive and anxiety symptoms in infertility women.
6. Which lifestyle, psychological factors and sources of stress increase the chances of a woman to be part of infertile group?
7. Analyze the relationship between work stress and school education among infertile women.

3. HYPOTHESES

I. Infertility is a chronic state of stress that is associated with anxiety and depressive symptoms, as well as high level of marital-, and work stress compared to fertile ones.

II. The psychological state (depression, anxiety, infertility-specific distress) of women undergoing assisted reproduction treatments is worse than non-ART counterparts.

III. Anxiety and depressive symptoms are associated with demographic (age, education) and infertility-specific factors (duration of infertility, numbers of ART) among infertile women.

IV. Anxiety and depressive symptoms are associated with infertility-specific distress (Social-, Sexual and Relationship Concerns, Rejection of Childfree Lifestyle, Need for Parenthood) among infertile women.

V. Anxiety and depressive symptoms are associated with general stress-resources such as financial-, mother related-, and health stress.

VI. Women' psychological well-being (depression, anxiety and financial-, mother related-, and health stress) is associated with infertility.

VII. Damaging to helath behaviour (smoking, more frequent alcohol consumption, unordinary BMI, lesser exercise) is more frequent in infertile women.

VIII. Infertility is more frequent among women with high level of qualification and work stress.

4. METHODS

1st study

Data

Our cross-sectional and pseudo-longitudinal studies were based on convenience sampling procedure used clinical and online setting. Data were collected between September 2013 and September 2014 in two Budapest-based private fertility centers (Kaáli Institute and Forgács Institute) and in the publicly funded Obstetrics and Gynecology Clinic No 2 of Semmelweis University. The study questionnaires were also available online on the web page of the Institute of Behavioral Sciences, Semmelweis University (http://meddoseg.magtud.hu/) as well as on a Hungarian website dedicated to reproductive health (http:\\teherbeeses.hu). Participation in the study was voluntary and anonymous. Informed consent was obtained from all participants before data collection. The selection criteria for the study were 1. fluent command of the Hungarian language, 2. female gender and 3. reproductive age (20-45). All women suffering from other chronic diseases (such as heart disease, autoimmune or hemorrhagic disease, diabetes, or hypertension) beyond infertility were excluded from the analysis. A total of 225 women participated in our study, 134 of them with primary infertility (6 recruited in a clinical setting and 128 online) and 91 fertile controls (26 recruited in a clinical setting and 65 online).

Measurement tools

The level of *trait anxiety* was assessed with the Hungarian version of the Spielberger State-Trait Anxiety Inventory. The Cronbach alpha value of this scale in our sample was 0,91.

The prevalence of *depressive symptoms* was assessed with the shortened Hungarian version of the Beck Depression Inventory (BDI). In our sample, this questionnaire yielded a Cronbach alpha score of 0,88.

Infertility-related distress was measured by the Hungarian version of the Fertility Problem Inventory (FPI). The original questionnaire was procured from the authors in English, and a Hungarian translation was created with their permission. The translation and re-translation was performed by the first author of this study and external collaborators, according to international guidelines. When comparing the two translations, we found their contents to be similar, which was also approved by the original authors. Cronbach alpha values for the subscales are (in order of the above appearance): 0,76, 0,81, 0,87, 0,80 and 0,74, respectively, while the full questionnaire yielded a Cronbach alpha value of 0,91.

Sources of stress were assessed with items using six-step (1-6) Likert scale responses. Prompted by the question "What sources of stress are present in your life?" the following responses were possible: "stress because my relationship is not harmonious 1) with my mother (hereafter, maternal relationship stress) 2) with my father 3) with my sibling(s) 4) with my partner 5) with my child(ren) 6) stress because of my illness (hereafter, illness stress) 7) stress rooted in my close relative's illness 8) stress because of financial problems".

Our test battery also included a record of *sociodemographic* parameters (age, place of residence, educational level, family income) as well as *infertility-specific parameters* (duration of infertility, participation in fertility treatments and the number of ART cycles (insemination or IVF-cycles).

Statistical analysis

Our descriptive analyzes reported frequency, mean and standard deviation. We also reported percentage differences between the variables.

By the type of variables, independent t-test and Khi-square (χ^2) test were used in the fertile vs. infertile groups. In the analysis, variables were used: age, age at first childbirth, years of education, per capita net income of the family, place of residence, duration of infertility, numbers of assisted reproduction treatment (insemination/IVF), depression, trait-anxiety. Independent t-test was performed in the infertile sub-group undergoing assisted reproduction treatment vs. non-ART group. In the analysis variables were used: depression, trait-anxiety and infertility-specific distress.

In order to identify underlying sources of depressive and anxiety-related symptoms we implemented a linear regression analysis with depression and trait-anxiety as dependent variables of two different models. In both models, independent variables were the following: 1. demographic variables: age, years of education; 2. infertility-specific variables: duration of infertility, numbers of assisted reproductive treatment; 3. subscales of the Fertility Inventory (Social Concern, Sexual Concern, Relationship Concern, Rejection of Childfree Lifestyle, Need for Parenthood); 4. sources of stress: stress because of financial problems (Financial Stress), perceived stress caused by the responders' relationships with their mothers (Maternal Stress) and stress resulting from the responders' experience of their own health and illnesses (Health Stress). Expression of the relationships was given by the standardized beta value (ß) obtained in the regression model with a 95% confidence interval (CI). Independent variables were added to the model using the 'Enter' method.

To assess whether the dependent variables [depression (BDI) and anxiety (STAI-T)] are assosiated with infertility in unadjusted and adjusted model (age, years of education, mother related, financial and health stress) under regression analysis, univariate ANOVA was used in infertile vs. fertile groups.

In order to eliminate the possibility that the psychological variables are partially overlapping constructs, the variance components of the results related to questionnaires were identified by Schmid-Leiman transformation (hierarchical factor analysis) and all result of questionnaires were tested by resident for this main component. In order to formulate hypotheses about the direction of causality in the revealed contexts, we carried out pseudo-longitudinal analyzes involving the duration of infertility.In the infertile sub-group the psychic distress indicators were resident for the duration of infertility and the resulting residues were compared with the value of the fertile group by univariate ANOVA. Expression of the relationships was given by the value of B obtained in the regression model with a 95% confidence interval (CI). Statistical analyses were conducted using the SPSS 20.0 for Windows. The traditional significance threshold of $p<0,05$ was used.

2 nd study

Data

Our analyzes were based on a merged database, which consisted of two studies: my sample date (see description of test sample I) and the most recent Hungarian epidemiological study ("Hungarostudy 2013") (Susanszky and Székely, 2013). The criteria for sampling here are in line with the objectives, in addition to the mentioned factors, in Study 1, was employment. In my research - along with the selection criteria - all HS 2013 data were merged with my own test sample. Participation in both studies was voluntary and anonymous. A total of 332 women participated in our study, 154 of them with primary infertility (4 recruited in a clinical setting, 141 online and 9 HS 2013 data) and 178 fertile controls (19 recruited in a clinical setting, 61 online and 98 HS 2013 data).

Measurement tools

Depressive symptom severity was assessed with the shortened Hungarian version of the Beck Depression Inventory (BDI). The Cronbach alpha value of the questionnaire in our sample was 0.89.

Marital stress was assessed with the shortened Hungarian version of the Stockholm Marital Stress Scale (SMSS). The Cronbach alpha value of the questionnaire in our sample was 0.66.

Work stress was assessed with the Hungarian version of the Effort-Reward-Imbalance Questionnaire (ERI). The Cronbach alpha values of the subscales were 0.81 and 0.82, respectively. Throughout the analysis, the Effort-Reward Index (and not the raw scale scores) was considered which had been computed as the ratio of efforts and rewards. A value over 1 is indicative of high workplace stress; therefore, subjects were grouped into one of the following two categories: high work stress (>1) or low work stress (0-1).

The test battery also included questions on *socio-demographic* variables (age, level of education: primary, secondary, and higher; and place of residence: village, city, capital), *infertility-related* ("Have you ever participated in infertility treatment (insemination or in vitro fertilization)?"), as well as *work-specific* (number of hours worked per day) and *lifestyle variables* (see detailed response options in Table 2). Alcohol consumption was measured by the question "How often do you consume alcoholic beverages?", smoking by the question "Do you currently smoke?", and physical activity by "How often do you do sports (e.g. swimming, cycling, aerobics)?". Body mass index was calculated on the basis of self-reported data on height and weight.

Statistical analysis

We compared the group of infertile and fertile women along demographic, lifestyle and psychological factors. Two-variable comparative analyzes were carried out with non-parametric tests: Mann-Whitney (MW) test (%) and Khi-square (χ^2) test. The relationships between medical and socio-demographic, infertility-specific, lifestyle and psychological factors were analyzed by multinomial logistic regression analysis. The examined factors (socio-demographic, infertility-specific, lifestyle and psychic), which were significantly differed on the two-variable level, were used as control factors. The odds ratios (OR) of the estimated value (estimate) were given with a confidence interval of 95% (CI). Statistical analyses were performed with IBM SPSS, version 20. The traditional significance threshold of $p<0,05$ was used.

5. RESULTS

1st study results

1. The mean age (M±SD) of the infertile population was younger than the fertile group (33.30±4.85 vs. 35.74±5.73, p=.001). However, one should note that, at the time of delivering their first child, fecund women were significantly younger than primary infertile women presently trying to conceive (28.08±5.03 vs. 33.30±4.85, p<.001).
2. No difference was detectable in education (61,19% vs. 62,64%, p=0,849): both groups displayed higher levels of schooling.
3. A larger income, however, was more frequent in the infertile group than in the fertile one (46,26% vs. 19,78%, p<0,001).
4. The mean values of depressive scores (14.94±12.90 vs. 8.95±10.49, p<.001) and anxiety (48.76±10.96 vs. 41.18±11.26,

p<.001) were significantly higher in infertile women when compared to fertile controls.

5. Involuntarily childless women were significantly more depressive (14.94±12.90 vs. 5.44±9.42, p<.001) and more anxious (48.76±10.96 vs. 45.37±7.97, p<.001) than the Hungarian female population of the same age group.
6. ART patients had significantly more depressive symptoms than infertile women with no fertility treatments (15.74±13.23 vs. 12.27±11.54, p<.05).
7. However, there was no significant difference between these groups in terms of trait anxiety (48.99±10.71 vs. 48.00±11.92, p=.350) and infertility-related stress (160.35±33.89 vs. 156.00±40.49, p=.196).
8. Trait anxiety was associated with age (ß=.142, p<.026), Social Concern (FPI-1) (ß=.315, p<.001), Sexual Concern (FPI-2) (ß=.303, p<.002), Financial Stress (ß=.173, p<.005) and Maternal Relationship Stress (ß=.162, p<.011), with a total explained variance of 62% (R^2=.615, Adjusted R^2=.575, p<.001)
9. Depressive symptoms were significantly associated with age (ß=.159, p<.018), Social Concern (FPI-1) (ß=.245, p<.003), Sexual Concern (FPI-2) (ß=.399, p<.001), and Maternal Relationship Stress (ß=.205, p<.002). The model explained 58% of the variance in depressive symptoms (R^2=.579, Adjusted R^2=.535, p<.001) among infertiles**.**
10. The B-coefficient of infertility before correction was 5.992 in the BDI model (95% CI: 2.784-9,200, p <0.001), in the STAI-T model it was 7.585 (95% CI: 4,619-10,552, p <0.001). The B-coefficient of infertility in age, education, maternal, disease, and financial stressed BDI model: 4.580 (95% CI: 1.479-7.681,

p=0.004) and 6.865 in the adjusted STAI-T model (95% CI: 4.065-9.665, p<0.001).

11. Results of pseudo-longitudinal analysis:

    The infertility B coefficient in the BDI model is 0.084 (95% CI: -0.138-0.403; p = non-significant) in the age-adjusted model 0.162 (95% CI: -0.125-0.428; p = non-significant). In the STAI-T model, 0.438 (95% CI: 0.219-0.746; p <0.001) in the age-adjusted model was 0.444 (95% CI: 0.176-0.713; p=0.001). In the financial stress model, -0.236 (95% CI: -0.499-0.039; p = non-significant), in the age-adjusted model -0.228 (95% CI: -0.504-0.048; p = non-significant). In the maternal relationship stress model, -0.377 (95% CI: -0.687- -0.157; p = 0.002) in the age-adjusted model was -0.401 (95% CI: -0.672- -0.129; p = 0.004). In the stress model of infertility as a disease, 0.007 (95% CI: -0.229-0.312; p = non-significant), in the age-adjusted model 0.035 (95% CI: -0.242-0.313; p = non-significant).

2nd study results

1. Women struggling with infertility problems were on average younger than members of the fertile group (33,66±4,69 vs. 37,64±4,56, p<0,001). However, it should be noted that, at the time of delivering their first child, fertile women were significantly younger than primary infertile women presently trying to conceive (33,66±4,69 vs. 24,37±4,37, p<0,001).
2. A higher proportion of college or university graduates was found in the infertile group than in the fertile one (62,75 % vs. 33,90%, p<0,001).

3. Infertile women with ART did not differ significantly from those without ART in their medical history: in both groups higher education (college or university graduates) is overrepresented (65.67% vs. 65%, $\chi 2$=0,883, p=0,643).
4. The mean value of depression (14,38 ± 12,78 vs. 5.59 ± 8,83, p <0,001) and level of work stress (1,37 ± 0,89 vs. 0,84 ± 0,49, p <0,001) was significantly higher in the infertile than the fertile group.
5. The two groups did not differ significantly in terms of marital stress (0,92±1,19 vs. 0,82±1,08, p=0,617).
6. 41,8% of the infertile compared to 13,6% of the fertile group (p<0,001), showed a combination of higher education and high work stress.
7. The number of working hours was significantly higher between the infertile than the fertile group (8,76 ± 3,33 vs. 8,10 ± 2,02, p <0,001).
8. Regarding to lifestyle factors, infertile women more frequently consumed alcohol (never 26,42% vs. 43,26%, ≤1/month: 41,56% vs. 37,64%, 2-4/month: 25,98% vs. 13,48%,>2/week: 5,84% vs. 5,62%, p=0,004) and were physically more active compared to their fertile counterparts (never 17,53% vs. 35,96% <than 1/week: 36,36% vs. 26,41%, 1 week: 16,83% vs. 12,92%, multiple times/week: 29,22% versus 24,72%, p=0,002).
9. There was no difference in body mass index (24,36 ± 5,38 vs. 24,40 ± 4,37, p=0,269) and smoking (never 57,52% vs. 59,70 %, previously: 26,80% vs. 19,32%, presently: 15,69% vs. 21,02%, p=0,189) between infertile and fertile women.
10. As revealed by the logistic regression model – accounting for 48% of the variance of the dependent variable – depressive symptoms

(OR=1,08 (CI=1,05-1,11), higher education (OR=3,20 (CI=1,14-9,00), and elevated work stress were associated with an increased risk of infertility, while age (OR=0,85 (CI=0,80-0,90) proved to be a protective factor in this model. Neither of the lifestyle factors (alcohol consumption p=0,564, exercise p=0,583) nor the interaction of educational attainment and work stress were significantly (p=0,667) associated with infertility.

6. CONCLUSIONS

1. Infertile women had higher level of socioeconomic status compared to their fertile counterparts which was accompanied by a higher level of work stress.
2. The psychological state of infertile women was worse than the fertile group, but the marital stress did not differ in the two groups.
3. Among women with ART treatment depressive scores are more frequent than non-ART infertile women (until the time of the survey). However, there is no significant difference between these groups in terms of anxiety and infertility-related stress.
4. Psychological distress (depression, trait-anxiety) related to infertility is increased by demographic (age) and infertility-specific factors (social and sexual concerns) as well as general source of stress (mother related-, financial stress). There was no association with distress in demographic variables (years of education), infertility specific variables (duration of infertility, numbers of ART procedure: insemination/IVF cycle), some subscales of Fertility Problem Inventory (relationship concerns, rejection of childfree lifestyle and need for parenthood), as well as general source of stress such as health stress.

5. According to the lifestyle factors, alcohol consumption and exercise was more frequent between infertile than fertile group. While smoking and body mass index did not differ significantly in the two study groups.
6. Higher level of work stress controlling by demographic, psychological and lifestyle factors was associated with infertility.
7. Based on our multivariate analysis, the higher level of education and the increased work stress were associated significantly with infertility.

Limitations of our studies

Based on cross-sectional studies, we can only draw conclusions referring to association and not causality. The conclusions of our pseudo-longitudinal analyses of causal inference are mere speculations, based on the assumption that psychological distress is associated with duration of infertility linearly. Because of the convenience sampling process,,our conclusions cannot be generalized, they only apply for our test sample. Another limit of our studies is that the range (20-45) of female fertile years left out of the analysis very young fertile and infertile women.. In this respect, the literature is not unified, the lower limit of fertile time being 15 years in some studies (Gurunath et al., 2011). In our studies we took into consideration not the biological, rather the social aspects of fertility. The problem of infertility comes up during long-lasting relationships, which usually begin around 20 years of age. The classification criteria of our sample (infertile vs. fertile) correspond to categorization methods used in previous studies (Domar et al., 1992; Kee et al., 2000; Kazandi et al., 2011), it should be noted that overlaps can also occur here. We pursued to study "unwanted childlessness", therefore considered the "intention of childbearing" as the relevant criterion

of infertility. This could theoretically include into the fertile group secondary infertile women who did not know about their infertility at the time of questioning (using contraception currently not giving them a chance to be aware of their potential fertility problems). Another limit is the suboptimal specificity of certain lifestyle measures (e.g., intensity of exercise, amount of alcohol consumed on one occasion), however, there is no unity in the literature in this respect either (Anderson et al., 2010; Sharma et al., 2013). I must mention as a further limit that we obtained a current picture about respondents' lifestyle habits. Therefore, we do not know if women had changed their behaviour because of the intent of conceiving a child in the infertile vs. fertile group. It is also noted that general sources of stress were measured with only one item (thoudh a Likert scale). However, there are known mental health studies (King, 2003; Lund et al., 2009) which also operationalized certain variables with only one question.

The strength of our studies

Our test sample consists of personal and online respondents, women undergoing ART and non-ART, as well (23.1% of the infertile group), the merged database also contributed to our heterogeneity. Our efforts to expand the size of our samples have contributed to a wider spectrum analysis of the psycho-social aspects of infertility than what can be found in the recent Hungarian literature. As a further strength, we can mention that we used general questionnaries to assess trait-anxiety (STAI-T) and depression (BDI), as well as infertility-specific distress (FPI), which it is novel in the Hungarian infertility research. In the Hungarian sample, we examined first the association of psychological and lifestyle factors related to infertility in a model. The main strength of our study is that pseudo-longitudinal analyses have provided new information about the relationship between

psychological factors (trait-anxiety, depression, mother-related, financial, health stress) and infertility among infertile women, regardless of duration of infertility and age. Based on our results, it can be further hypothesed that trait-anxiety and mother-related stress can play a role in the etiology of infertility. Empirical studies so far have given little attention to both the mother-related stress of infertile women and the association between higher education combined with high work stress and infertility.

7. LIST OF MY PUBLICATIONS

Publications related to the thesis:

Lakatos E, Pápay N, Ádám Sz, Balog P. 2014. Paradigmák a meddőség értelmezésében. Pszichológia, 34(3): 261-287.

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Lakatos E. 2016 A mentális egészség, az életmód és a termékenység összefüggése Magyar Pszichiátriai Társaság XX. Vándorgyűlése Budapest. poszter-előadás, 37.

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