RELATIONSHIP BETWEEN PRE-TREATMENT HABITUAL PHYSICAL ACTIVITY AND SUCCESS OF ASSISTED REPRODUCTION

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ABSTRACT. Introduction. The increasing incidence of infertility, the stagnation of success rates of its treatments, and the reasons for success vs. failure are current research topics both from psychosocial and lifestyle point of view. Objective. The aim of the study was to examine the effects of pre-treatment physical activity (PA) on the level of infertility-related distress and on outcome measures in women undergoing assisted reproductive therapy (ART). **Methods.** A prospective observational cohort study was carried out involving 45 female patients with infertility diagnosis in a university hospital-based fertility centre during March – July 2017 with the follow up of outcome measures in May 2018. Standardized psychological questionnaires and pre-treatment PA habits were administrated. **Results.** 60% of the women reported regular physical activity. 73.3% self-reported normal mood state (average 5.0±4.1) with BDI-13 and 91.1% self-reported normal level of distress (average 2.3±2,1) with GHQ-12. Moderately high stress by social concern (42.7±8.8) and very high stress level by sexual (39.2±6.5) and by relationship concern (48.4±9.1) of FPI was found. Significant difference between active and inactive group was described for PICS Self Regulating System (p= .034). Significant relationship between pre-treatment PA and successful pregnancy (p=.036) was found. **Conclusions.** Infertility specific scales provide more appropriate description on mental status of ART patients than general scales. Pre-treatment

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PA could positively affect success of ART. However, for more impressive results, detailed assessment of physical activity, increased number of participants, and further examinations are needed.

Key words: *physical activity, assisted reproduction, mental health, infertility-related stress, outcome measures*

Introduction and Hypotheses

A global prevalence of 12% to 15% of 1-year infertility was described by McLaren in 2012 (McLaren, 2012). In accordance with these notes the current annual European monitoring report of the European Society of Human Reproduction and Embryology (ESHRE) presents growing number of assisted reproductive therapy (ART), with the 640 144 cycles initiated in 2012 described more than threefold increase (3.14) in the number of cycles compared to the previous fifteen years and double (1.97) increase compared to ten years ago. However, for in vitro fertilisation (IVF) cycles the clinical pregnancy rates per aspiration and per transfer are stable with 29.4% and 33.8% respectively. Rates are similar for intra-cytoplasmic sperm injection (ICSI) with 27.8 and 32.3 %, respectively (Calhaz-Jorge et al., 2016).

The situation in the Hungarian fertile age population is quite similar, 10 to 15% of couples of fertile age struggles with fertility problems (Bernard & Krizsa, 2006) and the results after ART are also similar: 920 IVF and 3502 ICSI are conducted with 31.7% and 34.5 % of pregnancies per aspiration (Calhaz-Jorge et al., 2016). The increasing incidence of infertility, the stagnation of success rates of the treatments, reasons for success vs. failure are current research topics both from psychosocial and lifestyle point of view. It could be hypothesized that by decreasing the level of infertility related distress, abundance of pre-treatment moderate intensity physical activity will increase the success rate of ART. Therefore, the purpose of the present study was to examine the effect of physical activity (PA) and stress on success of ART.

Material and methods

A cross-sectional, observational cohort study was conducted with consecutive sampling using self-administrated questionnaire in paper-pencil form.

Data collection was carried out at the Assisted Reproduction Unit, Department of Obstetrics and Gynaecology, University of Pécs, Hungary. Patient enrolment into ART procedure was approved by two independent physicians. Participants were recruited into this study according to the date of the consultation. The routine examination on the 3rd day of the unstimulated cycles presented a good possibility to get in contact with the patients and invite them to participate. The test battery was given to 100 female patients and 45 has returned untill July 2017. The follow up of outcome measures was conducted in May 2018.

All female patients with both female and male factors of infertility who were indicated for fertility treatment (IVF/ICSI) were consecutively invited to participate in the study according to the following inclusion criteria. Participants had a BMI ≥ 18 kg/m² and ≤ 38 kg/m² and had any significant abnormality relevant to the ART procedure and outcome (metabolic and vascular diseases including diabetes mellitus, metabolic syndrome, fatty liver diseases and atherosclerosis, severe endometriosis (stage III or IV) and/or adenomyosis. Participants were not at significant risk of severe ovarian hyperstimulation syndrome (OHSS), were not diagnosed with major depressive disorder (MDD) or any other mental disorders, and had no significant physical or mobility impairments.

Assessment Scales

The variables of the conceptual framework were measured by a survey: self-reporting questionnaires were filled out at home in a conventional paper-pencil form. Questionnaires were returned at the 21st day of the unstimulated cycles.

Socio-demographic characteristics were obtained by using questions regarding age, educational level, income, marital status, duration of partnership, duration of infertility, BMI and lifestyle habits. Psychosocial characteristics will be assessed by measuring the domains of depression/subjective well-being, anxiety, perceived stress, and infertility-related stress. To identify PA and exercise habits in general, participants reported on the frequency of exercise.

A total score was computed from the General Health Questionnaire (GHQ-12) as a screening tool of mental health. It is used as the outcome index of psychological distress experienced within the past few weeks. This scale focuses on breaks in normal functioning rather than on life-long traits. The questionnaire is scored on a 4-point Likert-type scale, and the cut-off point was 5 to determine the respondents' level of psychological well-being (Goldberg & Blackwell, 1970).

Beck Depression Inventory (BDI-13) was applied for reporting respondents' mental health status. BDI is widely used to measure the intensity of depression in general population (Aaron T Beck, 1979; A. T. Beck & Beck, 1972; Aaron T. Beck, Steer, & Carbin, 1988; A. T. Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and in infertile patients as well (Khademi, Alleyassin, Aghahosseini, Ramezanzadeh, & Abhari, 2005; Smeenk et al., 2001). The questionnaire represents how the subject has been feeling in the last week. Each question has a set of at least four possible responses, ranging in intensity. A total score is computed and reflects the outcome index of depression. The validated Hungarian version of the short-form of the inventory with 13 items was completed by the respondents (Kopp & Fóris, 1993; Reynolds & Gould, 1981).

To examine infertility-related stress with a specific scale, the Fertility Problem Inventory (FPI) was queried. FPI is a 46-item questionnaire developed to measure the level of infertility-related stress (Newton, Sherrard, & Glavac, 1999). Patterns of infertility-related stress differed depending on gender, fertility history, and infertility diagnosis. The scale consists of five subscales identifying the following domains: social concerns (FPI1), sexual concerns (FPI2), relationship concerns (FPI3), rejection of childfree lifestyle (FPI4) and need for parenthood (FPI5). Permission for using validated Hungarian version of FPI was sent to the authors (Cserepes, Kollar, Sapy, Wischmann, & Bugan, 2013).

In line with positive psychology, Psychological Immune Competence System (PICS, also known as Psychological Immunity System Inventory – PISI) was applied. The questionnaire consists of 80 items and includes sixteen factors, which are divided into three subsystems: Approach Belief System, Monitoring-Creating Executing System and Self Regulating System. The subsystems are based on key psychological functions and refer to the mental resistance and adaptive coping capacity of the subjects (A Oláh, 2004; Attila Oláh, 2005).

Ethical approval

The study was reviewed and approved by the University Of Pécs, Clinical Center, Regional and Local Research Ethics Committee (Nr. 6955). Participants provided written informed consent prior to initiation of any study-related procedures, as shown by a signature on the Informed Consent Form. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Data analysis

Statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Normality of data distribution was tested by Kolmogorov-Smirnov test. Depending on distribution, Student t-test or Mann-Whitney U-test

were used to compare continuous variables. The association between two continuous variables was tested by Spearman's or Pearson's correlation coefficients and between two categorical variables was tested by chi square test. Multivariate analysis (logistic regression) was used to test the effect of psychological scales and PA on the two outcome groups. Data was expressed as mean ± SD and the significance level of $p<0.05$ was considered in each case.

Results

General characteristics

The major socio-demographic characteristics of the study population are presented in the first table. 45 female patients in reproductive age (33.2±5.4 years), with mostly normal weight (64,1%, BMI 18.5–24.9 kg/m2) participated in the study. They were sampled from a larger proportion with higher educational degree (46.7%) and with satisfactory economic status (87.5%). Each participant was either married or lived with a partner, and the duration of the partnership was 7.7±4.3 years on average with 3.1±2.0 years long child-wish.

Participants rated their health particularly good or very good, only 3 women reported 'fair general health' and another 3 women reported 'worse health during the treatment than before'. Participants experienced in average 5.0±2.9 psychosomatic symptoms during ART. In general, they self-reported a healthy lifestyle regarding diet, tobacco use and PA. Around 60% of them claimed to be physically active. We found various cases of infertility, duration and type of treatments. However, participants typically received IVF/ICSI (51.1%) with one year long (11.9±13.3 mounts) treatment because of female indication (33.3%).

Table 1. Socio-demographic data

Socio-demographic Data N=45	
Age (years)	
Mean (SD)	33.2 (5.4) 5.41)
Education	
Low	6 (13.3%)
Intermediate	18 (40.0%)
High	21 (46.7%)
Marital status (N=44)	
Married	24 (53.3%)
Partner	20 (46.7%)
Place of residence	
County seat	16 (35.6%)
City	15 (33.3%)
Village	14 (31.1%)

Income	
Completely satisfied	4 (8.9%)
Rather satisfied	31 (68.9%)
Rather dissatisfied	10 (22.2%)

Health Status and Lifestyle

BMI (kg/m2. N=39)

Mean (SD)	24.2 (5.3%) 5.32)
Underweight (<18.5)	2 (5.1%)
Normal weight (18.5–24.9)	25 (64.1%)
Overweight (25–29.9)	3 (7.7%)
Obesity (>30)	9 (23.1%)

Self-Rated Health - Before ART

Excellent	3 (6.7%)
Very good	16 (35.6.0%)
Good	23 (51.1%)
Fair	3 (6.7%)

Self-Rated Health - Undergoing ART

Much better	3 (6.7%)
Something better	7 (15.6.0%)
Same kind	32 (71.1%)
Somewhat worse	3 (6.7%)

Psychosomatic Symptoms

Mean (SD)	5.0 (2.9) 5.32)

Healthy Diet

Pay particular attention	6 (13.3%)
Pay some attention	31 (68.9%)
Not really	8 (17.8%)

Tobacco Use (N=44)

Heavy	0 (0.0%)
Light	10 (22.7%)
Non-Smoker	34 (77.3%)

Exercise (N=44)

Often	13 (29.5%)
Sometimes	14 (31.1%)

BDI_Categrories

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1,00	33	73,3	73,3	73,3
	2,00	8	17,8	17,8	91,1
	3,00	3	6,7	6,7	97,8
	4,00	1	2,2	2,2	100,0
	Total	45	100,0	100,0	

Not	17 (37.8%)

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Infertility	
Case of infertility	
Female	15 (33.3%)
Male	4 (8.9%)
Dual	2 (4.4%)
Undefined (by medical professionals)	8 (17.8%)
Unknown (to the respondents)	16 (35.6%)
Type of ART Treatment – at baseline (N=31)	
IVF/ICSI	23 (51.1%)
IUI	3 (6.7%)
OI	5 (11.1%)
Examination in progress	14 (31.1%)
Duration of the Treatment (months)	
	11.9 (13.3)
Mean (SD)	13.43)
	5.32)
Min - Max	0 - 48.0
Child-wish (years)	
	3.1 (2.0)
Mean (SD)	13.43)
	5.32)
Relationship (years)	
	7.7 (4.3)
Mean (SD)	13.43)
	5.32)

Psycho-social characteristics

GHQ-12 resulted in average 2.3±2.1 value. Only four patients exceeded cut-off point 5, indicating the presence of mental health disorder.

At BDI-13, 73.3% of patients self-reported normal mood state. However, the study revealed various levels of depression within the cohort: results revealed that eight women were living with mild-, three women were living with moderate-, and one woman was living with severe depression. By invitation to the study, psychological support was offered for every patient who deemed it necessary. In comparison with previous reports on community samples, we can claim that the mean 5.0±4.1 depression level of this ART population lies within the normal range (Freeman, Boxer, Rickels, Tureck, & Mastroianni, 1985; Hearn, Yuzpe, Brown, & Casper, 1987; Reading, Chang, & Kerin, 1989; Smeenk et al., 2001). (Table 2)
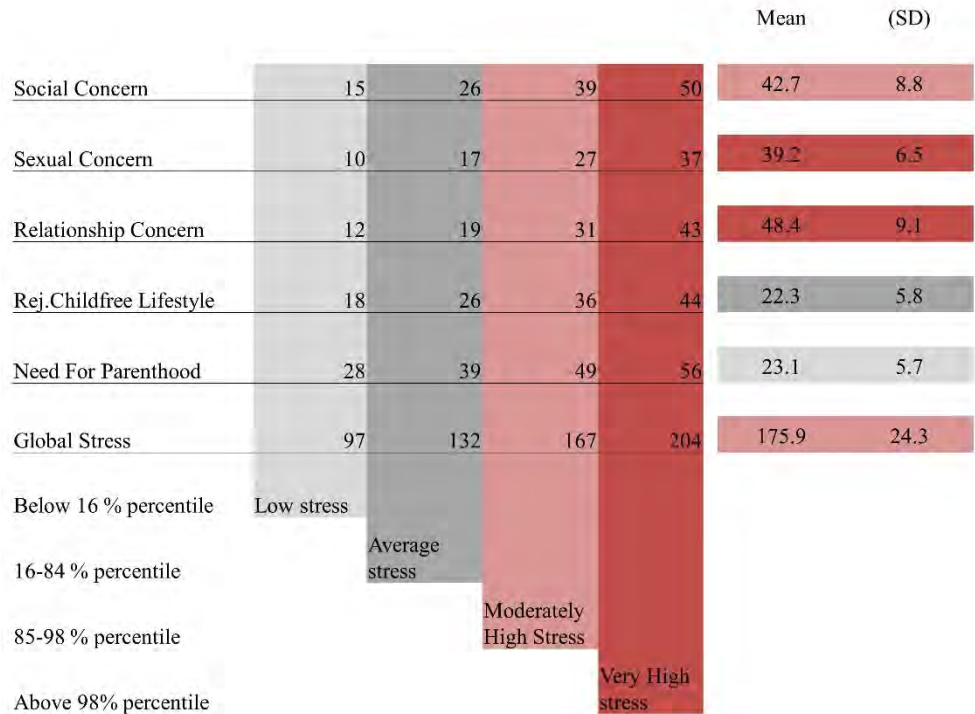
We examined the psycho-social variables (BDI-13, GHQ-12) according to the duration of treatment (less or more than 3 years), but we could not find any differences between the variables (BDI-13: $p=0.536$, GHQ-12: $p=0.803$).

Table 2. Pre-treatment psycho-social characteristics of women undergoing ART

Measure	Mean	SD	Median	Range	IQR lower	IQR upper
Child-wish (years)	11.9	13.3	6.5	48.0	.3	20.3
Duration of treatment (months)	3.2	2.0	3.0	8.5	2.0	3.9
GHQ-12 Score	2.3	2.1	2	10	1	3
BDI Score	5.0	4.1	5	18	2	7.5
Σ FPI	175.9	24.3	179.5	89.0	161.3	193.0
FPI1 Social Concerns	42.7	8.8	43.5	36	35	49
FPI2 Sexual Concerns	39.2	6.5	41	26	35	44.5
FPI3 Relationship Concerns	48.4	9.1	49	35	42	58
FPI4 Rejection of Childfree Lifestyle	22.3	5.8	23	23	18	25
FPI5 Need for Parenthood	23.1	5.7	24	22	17	27
Σ PICS	38.9	3.9	38.5	18.5	36.4	41.1
PICS Approach Belief System	13.7	1.6	13.6	6.1	12.4	13.6
PICS Monitoring-Creating Executing System	13.0	1.8	12.8	9.3	12.2	12.8
PICS Self Regulating System	12.0	2.2	12.3	9.0	10.5	12.3

For the purpose of measuring the level of infertility-related stress, a more specific tool, the FPI was applied and moderately high *Global stress* (175.9±24.3) was explored. In the five domains of the questionnaire we found low stress by *Need for parenthood* (23.1±5.7), average stress by *Rejection of childfree lifestyle* (22.3±5.8), moderately high stress by *Social concern* (42.7±8.8) and very high stress level by *Sexual-* (39.2±6.5) and by *Relationship concern* (48.4±9.1). Figure 1. Shows these results.

Figure 1. Infertility-related stress

Infertility related stress measured by Fertility Problem Inventory (FPI) in women undergoing assisted reproductive therapy (ART) (N=45)

Relationship between psycho-social characteristics and physical activity

Based on physical activity patterns, women were divided into two groups and means of baseline measures (child-wish, duration of the treatment and psycho-social scores) were compared regarding PA as the grouping variable (active/inactive). Results showed statistically significant difference between the groups only for PICS *Self Regulating System* (p= .034). (See in Table 3) *Synchronicity, Impulse control, Emotion control and Irritability control* belongs to this subsystem, which stabilize the person's inner emotional life and thus ensures the functioning of the first two subsystems.

Exercise Induced Differences in Psychological Health Domains in ART.

Table 3. Relationship between psycho-social characteristics and physical activity

Measure	Active		Inactive		
	Mean	SD	Mean	SD	p
Child-wish (years)	3.4	2.3	2.9	1.5	.980
Duration of treatment (months)	13.5	14.1	9.9	11.9	.453
GHQ-12 Score	2.6	2.5	2.1	1.9	.692
BDI Score	4.8	4.8	5.1	3.9	.422
Σ FPI	178.8	22.9	175.1	25.4	.660
FPI1 Social Concerns	45.1	7.2	41.3	9.6	.227
FPI2 Sexual Concerns	39.7	6.0	39.3	6.8	.894
FPI3 Relationship Concerns	47.6	10.7	49.3	8.0	.875
FPI4 Rejection of Childfree Lifestyle	22.8	6.2	22.1	5.8	.502
FPI5 Need for Parenthood	23.1	6.0	23.1	5.7	.979
Σ PICS	38.9	3.6	39.1	4.6	.502
PICS Approach Belief System	13.2	2.1	12.9	1.8	.283
PICS Monitoring-Creating Executing System	12.0	2.5	12.0	2.1	.772
PICS Self Regulating System	13.2	1.6	14.2	1.4	**.034***

During the follow up of outcome measures we received limited information for various reasons. Some patients continued the treatments elsewhere or interrupted the therapy. From the 38 known women six successfully conceived. All of the latter six women belonged to the physically active group. Positive significant relationship between pre-treatment PA and successful pregnancy (p=.036) was found.

In this sample neither univariate tests nor multivariate analysis showed any difference on pre-treatment psychological measures between the two outcome groups, which may possibly be due to the relatively small sample size.

Discussion

It was assumed that by decreasing the level of infertility related distress, abundance of pre-treatment physical activity will increase the success rate of ART. In our survey 60% of the women studied announced regular physical activity. Measured by general scales, 73.3% of the whole study population self-reported normal mood state (average 5.0±4.1) with BDI-13 and 91.1% normal level of distress (average 2.3±2,1) with GHQ-12. Regarding an infertility specific scale, moderately high stress by social concern (42.7±8.8) and very high stress level by sexual- (39.2±6.5) and by relationship concern (48.4±9.1) of FPI was found. Significant difference between active and inactive group was described for PICS Self Regulating System (p= .034). During the follow up of outcome measures only six successful pregnancies were be noted, all of which carried out by women who belonged to the physically active group. Positive significant relationship between pre-treatment PA and successful pregnancy (p=.036) was found.

Stress and female reproduction is an extensively investigated topic (Dobson, Ghuman, Prabhakar, & Smith, 2003; Ferin, 1999; Greil, 1997; Magiakou, Mastorakos, Webster, & Chrousos, 1997). Clinical and empirical research proved the notion that infertility is distressing and emotional instability due to grief and depression, anger, guilt, shock or denial, anxiety or loss of control influence the outcome of fertility treatments (Dunkel-Schetter & Lobel, 1991; Greil, 1997).

Smeenk et al demonstrated in a multicentre prospective study with survey methods that pre-treatment levels of perceived anxiety (P = 0.01) and depression (P = 0.03) are significantly positive related to treatment outcome in IVF/ICSI. Similarly to our results, they measured 5.6±5.1 BDI-13 scores in 291 women who reached embryo transfer (Smeenk et al., 2001). Their findings on the level of depression belong to the normal range of community samples (Freeman et al., 1985; Hearn et al., 1987; Reading et al., 1989; Smeenk et al., 2001). Jacob et al. investigated this particular question and took attention on studies that use standardized (general) scales on distress. Most of these found that the infecund patients are not significantly more clinically depressed than fertile controls (Jacob, McQuillan, & Greil, 2006). The only study with differing results was carried out by Domar et al., who reported the results of BDI-21 using cut-off score 9 (instead of the commonly recommended cut-off score of 21), and 13 when using for clinical diagnosis of depression. With the first they described 36.7% of participants were diagnosed with depression, and with the second scoring 8.4% of women studied were recognised as a person living with depression (Alice D Domar, Broome, Zuttermeister, Seibel, & Friedman, 1992).

To investigate the negative effect of pre-treatment levels of anxiety and depression on the outcome of IVF/ICSI, Smeenk et al. also administrated a *mixed method* study with 168 female patients. They compared the role of self-reports and endocrine variables, measured by concentration of adrenaline and cortisol, applying two general scales, BDI and State-Trait Anxiety Inventory (STAI) scales in ART. Similarly to their previous study, BDI scores were 5.4±4.7 in average. Significantly positive correlation was found between urinary adrenaline concentrations at baseline, embryo transfer (ET), and the scores on depression at baseline. By successful treatment, lower concentrations of adrenaline at oocyte retrieval and lower concentrations of adrenaline and noradrenaline at ET were observed. We extended our research with endocrine aspects in line with the work of abovementioned authors.

Kee et al. in their study on psychological strain in IVF compares average stress levels of 138 women with BDI. Women with unsuccessful IVF history had significantly higher level of depression than the IVF-success women (Kee, Jung, & Lee, 2000).We did not found differences in BDI 349ikcores in the two outcome groups p=747) Regarding the duration of infertility, BDI were moderately elevated in the first stage (< 3 years), authors described a decreasing trend in psychological stress with an advanced infertility duration. On depression scales, the intermediate and final duration of infertility patients showed less symptomatology than the first-stage patients. In our research we did not find differences in BDI scores between the two outcome groups or regarding the duration of infertility (p=0.536).

Cserepes and co-authors investigated the infertility-related stress in a Hungarian infecund population and examined the effects of gender roles, child wish motives, subjective well-being, and marital relationship on the experience of infertility according to the conceptual framework using a general (BDI) and a fertility specific (Fertility Problem Inventory (FPI)) scale as well. Depressive symptoms were correlated with infertility-related distress and fertility specific quality of life. In case of female patients, the researchers highlighted the importance of social (24.96±7.86) and relationship concerns (18.70±6.59) or rather the domain of need for parenthood 9(44.07±7.61) (Cserepes et al., 2013). In our study conflicting results were found, as social and relationship concerns triggered moderate and very high stress levels, whereas the need for parenthood remained on average level.

Another fertility specific instrument, the Fertility Quality of Life (FertiQoL) questionnaire was developed to reliably measure the impact of fertility problems and its treatment on quality of life (QoL) (Boivin, Takefman, & Braverman, 2011). Cserepes et. al conducted research using FertiQoL on

Hungarian sample and in cross-cultural comparison. Comparing fertility specific and general questionnaires can be found in the literature in relation to FertiQol-BDI (Cserepes, Korosi, & Bugan, 2014), FertiQol-Hospital Anxiety and Depression (HADS) (Aarts et al., 2011; Dural et al., 2016), FertiQol – WHOQOL (Boivin et al., 2011).

Impact of psychological interventions on pregnancy rates in infertile women is underlined by Domar et. al (A. D. Domar et al., 2000; A. D. Domar, Gross, Rooney, & Boivin, 2015). Other studies shift focus to lifestyle behaviours of women undergoing IVF and efficacy of mind/body intervention (A. D. Domar, Conboy, Denardo-Roney, & Rooney, 2012; A. D. Domar et al., 2011) In general, systematic reviews describe non-pharmacological interventions, such as exercise improving not only physical performance but other domains of quality of life (Francisco Meneses-Echavez, Gonzalez-Jimenez, & Ramirez-Velez, 2015; Kimmel, Haas, & Hermanns, 2014; Levine & Land, 2015; Mishra et al., 2012; Salakari, Surakka, Nurminen, & Pylkkanen, 2015).

We found a study on the connection between PA and psychological factors in IVF by Valoriani et al. Authors studied Hatha-yoga (HY) not only as exercise, but also as a psychological adjuvant, and found that women who are more distressed are more likely to accept psychological support before starting an IVF cycle and that in these women HY practice was associated with distress reduction ($p<0.0001$ for GHQ-12) (Valoriani et al., 2014).

PA appears to be beneficial during pregnancy as well. PA seems to reduce risks of gestational chronic diseases without adverse effects on the neonates (Downs, Chasan-Taber, Evenson, Leiferman, & Yeo, 2012; PAG, 2008; Pivarnik et al., 2006). In the absence of any contraindications following the American Congress of Obstetricians and Gynaecologists recommendations, pregnant women should engage in moderate intensity exercise for at least 30 minutes on most, if not all, days of the week (ACOG, 2002, 2015). However, there are no definitive physical activity guidelines for women attempting conception, particularly for the window of implantation and luteal phase. Most of the studies take attention to risk of frequent vigorous PA on fertility (Green, Daling, Weiss, Liff, & Koepsell, 1986; Wise et al., 2012) and on success of ART (A. D. Domar et al., 2012; Morris et al., 2006). To describe PA levels both instrumental and self-report studies were published.

In line with our findings on the benefits of pre-treatment activity, Moran et al. reported positive effect of lifestyle intervention including exercise and diet in conjunction with ART in overweight and obese women and described elevated successful pregnancy rate (12 / 18 vs 8 / 20) in the intervention group compered to controls (Moran, Tsagareli, Norman, & Noakes, 2011).

Conclusions

Infertility specific scales provide more appropriate description on mental status of ART patients than general scales. Pre-treatment PA could positively influence success of ART. However, for more impressive results, detailed assessment of physical activity, increased number of participants, and further examinations are needed.

Limitations

Results of this study are advised to be interpreted in light of the low number of research participants. Further research should explore the correlation between pre-treatment PA and infertility rates with larger sample size, applying more accurate measurement of moderate-intensity PA.

Possibilities for further research

The relationship between psychosocial stress and the release of adrenal hormones in relation to success of IVF/ICSI is still moderately discussed (Boivin and Takefman 1995). We intend to expand the current research to gain understanding on the biomedical point of view beside the psychosocial factors. This will provide the opportunity to compare the role of self-reports with endocrine variables.

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Conflict of interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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