

Doctoral School of Health Sciences

Faculty of Health Sciences, University of Pécs

Head of the Doctoral School: Prof. Dr. József Bódis MD, Ph.D., DSc.



EFFECTS OF PRE-TREATMENT HABITUAL PHYSICAL ACTIVITY
ON COURSE AND OUTCOME MEASURES OF
ASSISTED REPRODUCTIVE THERAPY

Doctoral (Ph.D.) thesis booklet

Viktória Prémusz

PR-5. Human Reproduction Programme

Programme leader:

Prof. Dr. József Bódis MD, Ph.D., DSc.

Supervisors:

Dr. habil. Ákos Várnagy, MD, Ph.D., Assisted Reproduction Unit, Department of
Obstetrics and Gynaecology, Medical School, University of Pécs

Dr. habil. Kinga Lampek, MSc, Ph.D., Department of Health Promotion and Public
Health, Faculty of Health Sciences, University of Pécs

Pécs, 2020

Introduction

Reproductive epidemiology

Similarly to other developed countries, the decline in the birth rate, the decrease in total population, and the increase in the average age of the population in Hungary pose a serious demographic challenge. The phenomenon in the 1980's was mainly due to the high mortality rate relative to other European countries, but since the 1990's it is due to low fertility rate. Since 1981, the population of Hungary has been steadily declining with varying intensity. According to the HCSO's Demographic Snapshot, after the absolute low point in 2011 (88 049), despite a slight increase, the number of live births still does not reach the level before the 2008 economic crisis (96 000). The total number of live births in 2018 was still very low, only 94 000, which is 46% decrease from 1978. Decreasing number of the population, with special regard on women in reproductive age and postponed childbearing raises the issue of increased incidence of disorders that impair fertility [KSH 206, KSH 2019, ACOG 2014].

Infertility is clinically defined as “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” in the International Classification of Diseases (ICD-11) [WHO 2018]. A global prevalence of 12% to 15% of 1-year infertility was described by McLaren in 2012 [McLaren 2012]. Although infertility rates remain unchanged over two decades, an increasing trend in fertility therapy was reported. From 1978 to 2012 a calculated total of 5 million, to 2018 approximately 8 million newborns, between 1% and 4% of all infants worldwide, have been born through ART [Bauquis 2012].

The monitoring report of the European Society of Human Reproduction and Embryology (ESHRE) presents a growing number of assisted reproductive therapy (ART). 776,556 cycles were initiated in 2014, which means an almost fourfold increase (3.82) in the number of cycles compared to 1997 (since ART data generated by national registries have been collected [Adamson 2018]). The number of treatments continues to expand and the contribution to the birth rates is still rising in Europe. 849,811 treatment cycles were reported in the reference year of 2015 and 918,159 in 2016 from 40 European countries [De Geyter et al. 2020].

Although the number of treatments is growing dynamically, for IVF cycles the clinical pregnancy rates (PR) per aspiration and per transfer were stable with 29.4% and 33.8% respectively, reported for 2012. Rates are similar for ICSI with 27.8% and 32.3 %, respectively [Calhaz-Jorge et al. 2016]. PR were marginally higher for IVF in 2014 than in 2013, at 29.9% and 35.8% versus 29.6% and 34.5%, and with ICSI 28.4 and 35.0% versus 27.8 and 32.9%, per aspiration and per transfer, respectively. PR for FER with own embryos continued to rise also, from 27.0% in 2013 to 27.6% in 2014 [De Geyter et al. 2020].

Quite similar situation was reported by Bernard and Krizsa in the early 2000s regarding the Hungarian fertile age population, as 10 to 15% of couples of fertile ages struggled with fertility problems [Bernard et al. 2006]. Similarly, 12% to 15% of fertility impairment was described in 2012 [McLaren et al. 2012] and age-standardized prevalence of secondary infertility (as the percent of women who seek a child aged 20–44 years) was reported in a World Health Organization (WHO) study as one of the highest with 18.0% (13.8%-24.1%) in Central-Eastern Europe in 2010 [Mascarenhas et al. 2012].

The results of ART in Hungary in 2012 were the following: 920 IVF and 3502 ICSI were conducted with 31.7% and 34.5 % of pregnancies per aspiration [Calhaz-Jorge et al. 2016].

Although the frequency of treatments increased from 2012 to 2014 (1179 IVF and 3857 ICSI were conducted in that year), ESHRE reported 25.0% and 28.8% of pregnancies per aspiration by ICSI and IVF, respectively.

In Hungary the National Health Care Service Center (NHCSC) [Állami Egészségügyi Ellátó Központ (AEEK)] – and before 2015, its legal predecessor the National Institute for Quality- and Organizational Development in Health Care (NIQODHC) [Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet (GYEMSZI)] – are responsible for data reporting on frequency, indication, type of procedure, and success rates of ART procedures.

During the five-year period between 2010-2014 most of the patients belonged to 30-34 years (34.89%) and 35-39 years (38.26%) age cohort and typically the first (48.95%) or second (27.25%) cycles were initiated at the institutions. 34.40% of the patients were diagnosed with female indications. Regarding the type of treatment, only IVF and ICSI data were consequently reported during the years; the number of cases increased by 28.71% and 31.72%, respectively, and the ratio of ICSI was approximately three-fold compared to IVF. Number of clinical pregnancies increased from 1649 to 1803 by 9.34% also. Pregnancy rate varies between 25.67%-32.36% per aspiration and between 28.72%- 35.14% per transfer, but an increasing tendency cannot be described. [Sources: https://www.aEEK.hu/documents/20182/607007/IVF_adatszolgaltatas_2010eves.pdf/079480aa-ff3b-51da-d8a7-595d174b9205; http://www.ijsz.hu/UserFiles/ivf_jelentes_2014.pdf]

Utilization of ART in Hungary

In case of assisted reproduction, we can compare social needs of fertility treatments with respect to the growth in number of annual cases. A preliminary study was conducted to assess the case numbers of assisted reproductive interventions in Hungary between 2010 and 2018 with regards to the type of intervention, patients, regional distributions, and form of financing. Cases were classified in fashion of the International Classification of Health Interventions (ICHI, earlier the International Classification of Procedures in Medicine ICPM), which is a code system containing a list of examinations and interventions eligible for outpatient care, used primarily for financial accounting, and also for patient documentation and professional data collection [WHO 2018]. Regarding ART investigations, follicle puncture (14703), embryo transfer (92722), intracytoplasmic sperm injection (97722), controlled ovarian hyperstimulation (97723), and assisted hatching (97724) were studied.

Our database was derived from the funding records of the National Health Insurance Fund (NHIF) [Nemzeti Egészségbiztosítási Alapkezelő (NEAK)]. In the period under review, until 1 January 2017, the health insurance organization and thereby the data provider was the legal predecessor of the National Health Insurance Fund (NHIF) [Országos Egészségbiztosítási Pénztár (OEP)]. The database covers the number of cases of infertility treatments between 2010-2018, accounted in the publicly funded and also in billable/chargeable form following Annex 9 of the 9/1993. (IV.2.) Decree of the Ministry of National Economy.

Cumulative number of cases increased by 61.39%, from 13 643 to 22 019 during the reference years as shown on Figure 5. Follicle Puncture (FP) (4 790 – 6 249) followed by Controlled Ovarian Hyperstimulation (COH) (3 351 – 6 419) were carried out in the largest number and the most dynamic rise was shown by Assisted Hatching (AH), with 126% increase. Mean age of patients was 35.564 years during this nine-year period, but it increased with 2.122 years from

2010 to 2018. As it was assumed 97.25% of the cases were covered by the standard medical care under Hungarian health insurance.

Regional and territorial distribution of the utilization of the treatments as described by the patient's residence shows a robust variance. During the studied timeframe most patients who received the interventions lived in Central Hungary NUTS 1 region. If we analyse the number of cases per 10 000 inhabitants by counties, utilization values of Baranya County (79.569) were significantly higher in 2018 compared to the national mean value (43.117). The amount of increase is worrisome in Baranya, where cases doubled compared to 2010. In addition to Baranya, Hajdú-Bihar, Tolna, and Somogy counties had outstanding utilization values as well.

The utilization data of fertility interventions demonstrate the changing patterns and the importance of fertility treatments well.

Efforts to improve success rates

Despite all micromanipulation, microsurgery, and embryo transfer techniques, pregnancy and birth rates are far behind expectations. Efforts were also made by the Human Reproduction Scientific Research Group of the Hungarian Academy of Sciences – University of Pécs to improve success rates of ART. The main task of the research group since 2012 has been to detect and investigate potential biomarkers for ART from both the follicular fluid surrounding the oocyte and the culture medium of the human embryo. The research is focused on the identification of biomarkers that may indicate embryo viability, implantation ability, and genetic intactness [Bódis et al. 2015]. After learning about the above biomedical aspects on to improvement of success rates, with respect to former research experience on the importance of PA on female health [Szalai et al. 2014, Szalai et al. 2015, Perjés et al. 2017] we decided to shift the focus of the current study from the main field of the research group, under the guidance of Dr Ákos Várnagy and Dr Kinga Lampek. Our research interest turned to psychosocial and lifestyle factors, with the aim to extend investigation methods with a multicausal approach.

Physical activity (PA) and health status

During our analysis, we considered physical activity (PA) as an emphasized lifestyle aspect. PA is an important factor among the determinants of health due to its protective factor and preventive role [Piercy et al 2020]. More than half of the Hungarian population is overweight, and two thirds do not do sports regularly [Ács et al. 2018, OGYEI 2014]. Such behaviours have been associated with chronic metabolic and musculoskeletal disorders such as type two diabetes, hypertension, obesity, and coronary heart disease, as well as psychological impairments and imbalanced mental health status [Watson et al. 2017, Ostojic et al. 2011].

The World Health Organization (WHO) guidelines and recommendations state that to maintain health, adults younger than 65 years old should perform at least 150 minutes of moderate intensity PA or at least 75 minutes of vigorous intensity PA throughout the week. For additional health benefits, adults should increase moderate-intensity PA to 300 minutes per week, or equivalent. In this case PA has been defined as “any bodily movement produced by skeletal muscles that results in energy expenditure” [WHO 2018, Lee et al. 2012]. Regarding females, the strategy of the WHO only highlights that member states should provide information about the importance of PA during pregnancy about the benefits of being physically active and of maintaining a healthy body weight prior to and during pregnancy, including during antenatal

classes. It suggests risk assessment and screening approaches to identify pregnant women requiring more support for behavioural change [WHO 2018].

In the case of female reproduction, the American Obstetrics and Gynecology Association's (ACOG) recommendation of PA for 150 minutes per week is noteworthy, suggesting moderate PA of 20-30 minutes almost every day of the week [ACOG 2015] that can help prevent pregnancy diabetes mellitus, preeclampsia, and chronic musculoskeletal disorders; maintain a healthy weight; and improve mental health [Russo et al. 2015, Tendais et al. 2010]. In contrast, the recommendations of the American Sports Physicians Association (ACSM) and the World Health Organization (WHO) not only count exercise for the recommended 150 minutes per week, but also consider all physical activity that involves energy [ACSM 2006, Waxman et al. 2004]. PA should therefore also include activity in leisure or recreation, or in other areas of life such as transport (active transport) or work (as a professional). Particular emphasis should be placed on PA during housekeeping, domestic work, child-rearing, caring for the elderly or sick when examining pregnancy [Watson et al. 2017, Borodulin et al. 2008].

Theoretical framework of the dissertation

Following the opinion of Lakatos et al, couples with infertility problems should become familiar with the adverse effects and should take steps to manage and change them. Therefore, in addition to the medical diagnosis, non-biological aspects of the reproductive dysfunction may be just as important as environmental factors, psychosocial distress, negative judgement, impact of diagnosis, negative consequences of interventions or non-adaptive coping. To ensure successful reproduction, monitoring of and disarming the negative psychological factors are necessary [Lakatos et al. 2014].

Using the above-mentioned theoretical framework, a multi-causal model was developed, which does not only consider the biomedical and psychosocial factors, but also focuses on the importance of lifestyle and in particular, PA. Please find the detailed model with all variables studied in the thesis.

Aims

The overall aim was to investigate the effects of pre-treatment habitual physical activity on course and outcome measures of assisted reproductive therapy.

Specific aims

- To analyse the utilization of assisted reproductive treatments in Hungary.
- To investigate the relationship between self-reported frequency of exercise and success of assisted reproduction in a pilot study.
- To explore in a qualitative synthesis of a systematic literature review on appropriate measurement methods of physical activity in association with ART.
- To assess the effects of psychosocial and lifestyle factors with special regard to physical activity on course and outcome of ART.

Sub-study 1

Pilot study - Relationship between self-reported frequency of exercise and success of assisted reproduction

It was assumed that by decreasing the level of infertility related distress, abundance of pre-treatment physical activity may increase the success rate of ART.

A cross-sectional, observational cohort study was conducted with consecutive sampling using a 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, Baranya County, 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 until July 2017. The follow-up of outcome measures was conducted in May 2018.

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.

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 were 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 [Goldberg et al. 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 [Beck et al. 1961, Beck et al. 1972], and in infertile patients as well [Kopp et al. 1993, Smeenk et al. 2001]. To examine infertility-related stress with a specific scale, the Fertility Problem Inventory (FPI) was queried [Newton et al. 1999, Cserepes et al. 2013]. In line with positive psychology, Psychological Immune Competence System (PICS) was also applied. [Oláh 2004, Oláh 2005].

The study was reviewed and approved by the University of Pécs, Clinical Center, Regional and Local Research Ethics Committee (Nr. 6955). 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. Data was expressed as mean \pm SD and the significance level of $p < 0.05$ was considered in each case.

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. Participants typically received IVF/ICSI (51.1%) with one year long (11.9 ± 13.3 months) treatment because of female indication (33.3%).

In this preliminary 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 groups was described for PICS Self Regulating System ($p = 0.034$). During the follow-up of outcome measures only six successful pregnancies were noted, all of which were carried out by women who belonged to the physically active group. Positive significant relationship between pre-treatment PA and successful pregnancy ($p = 0.036$) was found.

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.

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.

Sub-study 2

Qualitative synthesis - a systematic literature review on measurement of physical activity in association with ART

The aim of this sub-study is to select the most appropriate method of measuring physical activity in the context of assisted reproduction by qualitative synthesis of a systematic literature review.

The systematic review was based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria [Moher et al. 2009] which provides a clear protocol over traditional literature reviews analysing as much of the literature as possible in a non-selective, bias-free, and reproducible way with respect to a given research topic. Although PRISMA is primarily used for the analysis of randomized controlled clinical trials, it can also be used as a basis for reporting other types of studies [Kamarasi et al. 2015].

We continued our research in the Web of Science, Medline (PubMed), Cochrane Library, and Science Direct databases, as well as through additional search. During the search we focused on the words as physical activity, exercise, human, assisted reproduction and In Vitro Fertilization. A selection of English-language studies published over the last 15 years was selected for the analysis, with the last search conducted in January 2019.

The 398 related studies found were reviewed by two independent researchers, with a third opinion involved in case of disagreement. After applying the exclusion criteria (non-relevant/different to the research topic and non-human subjects), 53 results were identified, of which further 24 were excluded after reading the abstracts with respect to parallelism, different exposure, and research subject. Finally, 17 in extenso publications were examined, 9 of them were relevant and included in the qualitative synthesis.

The total number of patients studied in the 9 studies involved in the qualitative study was 3404. We found a total of 5 specific questionnaires used in interview or self-report to measure physical activity in relation to fertility treatments. Based on our preliminary studies on the measurement of physical activity and its role in female reproduction, the use of questionnaires, the data based on international comparisons, the availability of questionnaires, and the availability of a validated Hungarian version, it can be concluded that the IPAQ-SF and GPAQ questionnaires combined with an accelerometer seem to be the most appropriate ones, which seems effectively contribute to the future development of a PA recommendations prior to ART treatment.

Main study

Effects of psychosocial and lifestyle factors with special regard to physical activity on course and outcome of ART

Introduction

The increasing incidence of assisted reproductive therapies (ART) and unchanged success rates highlight the need for inspection of social, psychological and lifestyle covariates. To examine the impact of interventions or health conditions in a broader context we applied the general quality of life (QoL) concept of the WHO, defined as “people's perception of their position in life in the context of the culture and value systems in which they live in relation to their objectives, expectations, standards and concerns” [WHO 1995]. This comprehensive framework involves physical and psychological health aspects as well as social relationships, environment and spiritual aspects and widely used on subjects with different conditions, inter alia in infertility [Chachamovich et al. 2007]. The failure to become pregnant may specifically affect various life dimensions such as depression, anxiety, social isolation, sexual dysfunction, social and psychological distress, and poorer marital adjustment [Rashidi et al. 2008].

It has also been hypothesized that depression and anxiety may negatively affect female reproduction or ART due to hormonal, neuroendocrine, or immunologic functioning and lead to poor outcomes [Dobson et al. 2003, Lynch et al. 2014]. The relationship between psychosocial stress (PSD) in relation to the success of IVF/ICSI is still moderately discussed [Boivin et al. 1995].

Benefits of regular physical activity to maintain physical, mental and social health is not called into question [WHO 2018]. Depending on intensity or duration, certain studies disagree on the health effects of exercise or even PA in relation to ART [Rich-Edwards et al. 2002, Morris et al. 2006, Paloma et al. 2014, Rao et al. 2018]. These studies primarily focus on outcomes of ART and less on the QoL and PSD aspects on the course.

Therefore, the aim of the current research was to describe PA, QoL and PSD patterns and their relationships in ART patients on the course and outcomes of the treatment.

Methods

A cross-sectional, observational cohort study was conducted with consecutive sampling at the Assisted Reproduction Unit, Department of Obstetrics and Gynaecology, University of Pécs, Hungary. All female patients with both female and male factors of infertility who were indicated for fertility treatment (IVF/ICSI) in the institute were consecutively invited to participate in the study. Participants were recruited according to the date of the fertility consultation. Inclusion criteria were BMI ≥ 18 kg/m² and ≤ 38 kg/m², 18 to 40 years of age, having undergone not more than three unsuccessful cycles and no significant health risk 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 diagnosed with any mental disorders and had no significant physical or mobility impairments.

Data collection was carried out during the routine examination on the 3rd day of the unstimulated cycles. 62 women participated in the study between December 2018 and June 2019, which means 82.66% response rate. Self-administrated questionnaires were given to participants, who filled them at home in a conventional paper-pencil form. Questionnaires were returned on the

21st day of the unstimulated cycles. 2 participants were excluded due to high rate of missing questionnaire data.

Assessment scales

Socio-demographic characteristics were obtained using questions regarding age, educational level, income, marital status, duration of partnership, duration of infertility, BMI and lifestyle habits.

Quality of life was measured in general and as infertility-related quality of life as well. The validated Hungarian version by Paulik et al. of World Health Organization Quality of Life-BREF (WHOQOL-BREF) general questionnaire and the Core and Treatment modules of the Fertility Quality of Life Questionnaire (FertiQoL) were used. [WHO 1998, Paulik et al. 2007, Boivin et al. 2011].

As in the pilot study, Beck Depression Inventory (BDI-13) was applied again for reporting respondents' mental health status [Beck et al. 1961, Beck et al 1972, Reynolds et al. 1981, Kopp et al. 1993]. To examine infertility-related distress with a specific scale, the Fertility Problem Inventory (FPI) was included. The former Hungarian version [Newton et al. 1999, Cserepes et al. 2013] was accurately redefined, results will be published separately.

Assessment of PA

To describe PA and exercise habits, participants self-reported on the type and frequency of exercise in a PA diary and reported all kinds of physical activity in two types of PAQ. These self-reports were compared with objective measures collected by the Triaxial ActiGraph GT3X+ accelerometers.

International Physical Activity Questionnaire (IPAQ-SFH)

The IPAQ-SF is a single domain questionnaire, 7 items surrounding last 7-day recall of PA and reports on types of intensity of PA and sitting time [Craig et al. 2003, Lee et al. 2011, van Poppel et al. 2010]. The data were expressed in min/week and was summarised in moderate and vigorous activities min/week, MVPA min/week, and sitting time min/week also. [IPAQ 2005]. The Hungarian version of the questionnaire (IPAQ-SFH) is under validation by the EUPASMOS project on Hungarian general sample [Nash et al. 2018].

Global Physical Activity Questionnaire (GPAQ-H)

The GPAQ version 2 used in our research was developed by the WHO. This self-administered form comprises 16 items that measure the physical activity levels of a typical active week (7 days) of adults. The questionnaire contains three domains of PA: work, transportation, and recreational activities. The duration and frequency of physical activity (min/day) were recorded in case of all three abovementioned domains. According to intensity, moderate and vigorous activities can be classified and walking activities should be also distinguished. Results were expressed in time (minutes) or in energy expenditure (MET: Metabolic Equivalent of Task). Total MVPA min/week (all vigorous + all moderate activities' mins), moderate and vigorous activities in min/week, and weekly sitting time in min/week values were calculated [WHO 2012, Herrmann et al. 2013]. The cultural adaptation, efficient translation, and validation of the Hungarian version were composed by our scientific research group [Armstrong et al. 2006, Clealand et al. 2014, Ács et al 2020].

Accelerometry monitoring

Triaxial ActiGraph GT3X+ accelerometers (ActiGraph, Pensacola, FL) were used to collect data on PA with standard device initialization (sample rate of 30Hz, 60 second epochs and normal filter option).

Participants were instructed to wear the accelerometer on the right hip (near the iliac crest) for a week, from the time they woke up in the morning until they retreated at the end of the day, except for the duration of any water-based activities, such as swimming or bathing. The Actigraph GT3X + device measures the strength of the movement in three spatial directions, as well as their duration.

60 or more motionless minutes was defined as “non-wear time”. A minimum of 480 minutes of wear-time was required daily and a minimum of 5-7 days with valid wear time including at least one weekend day was required for inclusion in the analysis [Troost et al. 2002]. ActiLife 6 software was used to initialize the accelerometer and to download results, and raw data was converted with Freedson cut points [Freedson et al. 1998].

Based on the additional physical activity diaries any contact sports or water-based activities were performed, which may restrain the participants to wear the accelerometer. Although, four participants were excluded due to invalid wear-time. The average number of valid days was 6.32.

Physical Activity Categories by Guidelines

On the basis of the results, physical activity was categorized by meeting the key guidelines of PAGAC for adults as Inactive (any activity beyond basic movement from daily life activities), *insufficiently active* (less than 150 minutes of moderate-intensity physical activity (MPA) or 75 minutes of vigorous-intensity physical activity (VPA) or the equivalent combination of them per week), *active* (equivalent of 150 minutes to 300 minutes of MPA a week), or *highly active* (more than 300 minutes of MPA a week) [HHS PAGA 2018].

Following the ACOGs recommendations, pregnant women should engage in *moderate intensity exercise for 150 minutes* per week [ACOG 2002, ACOG 2018]. However, there are no definitive physical activity guidelines for women attempting conception, particularly for the window of implantation and luteal phase. We integrated this into our model, and application of this category was confirmed with the similarity of PA patterns of ART patients to women during gestation.

Most of the studies draw attention to risk of frequent or vigorous PA on fertility [Wise et al. 2012, Gudmundsdottir et al. 2009] and on success of ART [Morris et al. 2006, Domar et al. 2012]. Therefore, *exercising 240 minutes* or more per week was considered an independent category.

Fertilization protocol

Publications of the Human Reproduction Scientific Research Group by Bódis and Várnagy described the detailed protocol of fertility treatments as follows [Bódis et al. 2015, Várnagy et al. 2018, Gödöny et al. 2014].

Ethical approval

This study was approved in advance by the University of Pécs, Clinical Centre, Regional and Local Research Ethics Committee (Nr. 6533). Each participant voluntarily provided written informed

consent before participating. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Data analysis

Statistical analyses were performed using IBM SPSS Statistics 25.0 for Mac (SPSS Inc., Chicago, IL, USA). Normality of data distribution was tested by Kolmogorov-Smirnov test. Mann-Whitney U-test was used to compare continuous variables. The association between two continuous variables was tested by Spearman's rank correlation. To define predicting factors of primary and secondary outcomes of IVF from pre-treatment habitual PA, psycho-socio-demographic and baseline biomedical variables, we conducted a multivariate linear regression using the stepwise method. Logistic regression analysis was conducted to evaluate the effects of all the above parameters on livebirths. A post-hoc statistical power analysis was performed using G*Power software, version 3.1.9.6 for Mac (Franz Faul, Christian-Albrechts-Universität Kiel, Kiel, Germany) [Faul et al. 2007]. Data was expressed as mean \pm SD as well as medians with 25th and 75th percentiles and the significance level of $p < 0.05$ was considered in each case.

Results

General characteristics of the sample

Sixty female patients in reproductive age (34.6 ± 5.2 years), with mostly normal weight (70.0%, BMI $18.5\text{--}24.9$ kg/m²) participated in the study. They were sampled from a larger proportion with higher educational degree (58.6%) and with satisfactory economic status (96.6%). 95.0% of them worked and 75.0% had urban residence. Each participant was either married or lived with a partner, and in average the duration of the partnership was 8 years (7.6 ± 3.8) with an around 5-years-long (59.0 ± 38.4 month) child-wish. We found various cases of infertility, duration and type of treatments. However, these primarily nulliparous women (84.4%) typically received IVF/ICSI (82.3%) with mostly non-male indication (75.6%). Complete clinical data was available regarding 45 IVF/ICSI patients.

76.7% of the participants rated their physical health particularly good or excellent. In general, they self-reported a health-conscious lifestyle regarding diet, tobacco use and PA, and quality of sleep was satisfactory (86.2%) as well. Lifestyle change was also examined, but we cannot report relevant changes back to 5 years ago, from the beginning of ART, or in the current month. 50.0% of the participants claimed to be physically active, one tenth of them exercised 4-7 times per week.

General and infertility-related quality of life

Based on the WHOQOL-BREF which examines general QoL, 70.00% of the respondents self-reported good or very good health and 78.33% of them was satisfied or very satisfied with her QoL. Respondents were less satisfied with Psychological Domain (67.75 ± 13.13) and most satisfied with Physical Health Domain (75.22 ± 14.95) of their QoL.

For the purpose of measuring the level of infertility related QoL, a more specific tool, the FertiQoL was applied. We found similar values with this specific scale like with WHOQOL-BREF. In the four Core subscales of the questionnaire we found lower QoL by the Emotional Scale (59.51 ± 20.09) and the Mind-Body Scale (62.85 ± 20.93), mediate QoL by the Social Scale (69.72 ± 19.38) and moderately better values by the Relational Scale (77.22 ± 17.70). Respondents

already receiving ART treatment rated their QoL referring the interventions equally in both Treatment subscales: Environment Scale (67.31 ± 18.27) and Tolerability Scale (66.70 ± 23.83). Subscales were summarised and similar values were found by the Core Scale 67.33 ± 15.75 and the Treatment Scale 67.07 ± 17.50 .

General and infertility-related distress

The validated Hungarian short-form of the Beck Depression Inventory (BDI-13) was applied to reflect on distress in general. 68.96% of the respondents scored less than 5 points, which indicates normal mood state; and 20.68% belonged to the category of mild depression (6-11 points). Two patients reported severe depression.

For the purpose of measuring the level of infertility-related stress, FPI was applied and moderately high *Global stress* (183.33 ± 28.19) was explored. In the five domains of the questionnaire we found similar values as in the pilot study: average stress by *Rejection of childfree lifestyle* (23.25 ± 6.04), moderately high stress by *Social concern* (41.40 ± 9.84) and very high stress level by *Sexual-* (38.62 ± 7.77) and by *Relationship concern* (48.53 ± 9.68). Stress related to *Need for parenthood* was low again, but markedly higher than in our first pilot study (31.68 ± 8.35 vs 23.1 ± 5.7).

Physical activity patterns

Regarding GPAQ-H respondents performed an average of 461.50 ± 785.56 min/week moderate and 158.00 ± 467.34 min/week vigorous PA in work and only 35.00 ± 82.70 min/week vigorous activity in recreation/leisure time domain. However, medians (0.00) revealed, that vigorous PA during work or leisure time are not common in the studied group. They preferred moderate-intensity recreational activities for 2 hours per week (124.80 ± 339.56).

Nevertheless, they spent 268.75 ± 521.77 min/week on average with active transportation, for example with walking or cycling, which covers 806.25 ± 1565.30 MET energy expenditure. They spend 6.53 hours per day sedentary (2745.17 ± 1755.39 min/week).

Analysing the data by intensity, we found that respondents spent 786.32 ± 998.92 minutes (2910.65 ± 3932.02 MET) with moderate to vigorous activities (MVPA). In total, considering all types and intensities of activities lasting more than 10 minutes, women performed around 16.98 hours (1018.95 ± 1225.72 min/week) or 3716.90 ± 4588.16 MET PA.

Regarding the ActiGraphs, light activity was the most characteristic with 1239.87 ± 329.50 min/week, moderate (233.35 ± 132.00 min/week) and vigorous activities (4.65 ± 13.27 min/week) lag behind the subjective measures, very vigorous activity was almost negligible (3.70 ± 15.73 min/week). They performed around 4 hours MVPA (241.70 ± 145.10 min/week) and took in average 7060.28 steps daily (49422.73 ± 16351.52 counts/week) based on objective measures.

Comparing the data of the three measurements, we found significant differences between the two subjective instruments and the objective measures in all of the marked scores except for moderate PA and MVPA means between Accelerometer and IPAQ-SFH ($p=0.468$, $p=0.433$ respectively) and vigorous means between Accelerometer and GPAQ-H ($p=0.255$). The GPAQ-H and IPAQ-HL questionnaires showed similar mean differences, but the overestimation of moderate activities and MVPA was higher in GPAQ-H, and of vigorous activities in IPAQ-SFH.

If we categorise their performance, 27 women (60.00%) reported notable leisure time PA, and only 18 of them (40.00%) reached the 150 min/week RMPA recommendation. 9 (20.00%)

persons spent more than 240 minutes/week with recreational type PA, just like in the PAGA Highly active category.

Relationship between quality of life aspects and PA

For detecting the relationship between pre-treatment physical activity patterns and quality of life of IVF patients, IPAQ-SFH and accelerometer data proved to be less informative. Regarding correlations between the IPAQ-SFH and any of the QoL's domains, relationship was only found with the following baseline factors: between age and amount of total PA in min/week ($R=0.309$, $p=0.046$) and expressed in METs ($R=0.305$, $p=0.049$), and between BMI and MVPA minutes and METs ($R=0.331$, $p=0.032$). Similar weak results were found in case of ActiGraph data. BMI was positively correlated with Light intensity activities ($R=0.399$, $p=0.043$), but no more relationship could be described. Amount of PA increased in line with years and also with BMI, suggesting more of a health-conscious behaviour by women exposed to higher risk.

With GPAQ-H more impressive finding could be described. Relationship between the same baseline biological factors and PA has been confirmed by GPAQ-H. Age strongly correlated with VPA minutes and METs ($R=0.501$, $p=0.001$), MVPA total min/week ($R=0.371$, $p=0.015$) and MET ($R=0.425$, $p=0.006$) also with the cumulative values of all PA total minutes ($R=0.415$, $p=0.007$) and METs ($R=0.440$, $p=0.004$). BMI also correlated with Active transportation minutes ($R=0.408$, $p=0.007$), MVPA minutes ($R=0.363$, $p=0.018$) and METs ($R=0.330$, $p=0.035$) and also with total minutes ($R=0.446$, $p=0.004$) and total METs ($R=0.436$, $p=0.004$).

Regarding general QoL scores, strong correlations were found by WHOQOL-BREF between Psychological Domain and time of vigorous recreational activities ($R=0.484$, $p=0.001$) and energy expenditure of recreational activities ($R=0.428$, $p=0.006$), and significant correlation with weekly time spent with recreational activity ($R=0.319$, $p=0.039$).

Similar correlations could be detected between the specific FertiQoL Core Scale's Mind-Body domain and Total METs ($R=0.336$, $p=0.024$). Tolerability Subscale also correlated with the total MET of active transportation ($R=0.266$, $p=0.044$). The most positive relationship was found between Total MET and the following subscales and scores of FertiQoL: weak correlation was found with Core Score ($R=0.272$, $P=0.041$) and more robust with Environment Scale ($R=0.384$, $p=0.003$), Tolerability Scale ($R=0.371$, $p=0.004$), Treatment Score ($R=0.390$, $p=0.003$) and Total Score ($R=0.345$, $p=0.009$).

Relationship between psychosocial distress aspects and PA

Relationship between general PSD, measured with BDI and PA patterns cannot be described. Our results on GPAQ-H revealed, that recreational PA could counteract with some aspects of infertility related distress, since time spent with moderate RPA, total time and total MET of RPA negatively correlated with Social Concern ($R=-0.378$ $p=0.013$, $R=-0.386$ $p=0.012$ and $R=-0.360$ $p=0.023$ respectively) and Relationship Concern of FPI ($R=-0.365$ $p=0.019$, $R=-0.368$ $p=0.018$ and $R=-0.342$ $p=0.033$ respectively). However, time spent with vigorous RPA was also significantly correlated to 'Rejection of childfree lifestyle' ($R=0.354$ $p=0.021$). A relationship similar to the above cannot be described by IPAQ-SFH or ActiGarph.

Relationship between IVF outcomes and physical activity

If we divided IVF patients regarding the presence of clinical pregnancy as the primary outcome, we can conclude that PA patterns differ. Due to high SD, we could detect a significant difference only in case of GPAQ-H recreational PA MET means ($p=0.048$). Minutes spent with recreation per week also showed tendency-like difference, but a level of significance was not reached ($p=0.067$). In both cases, means of the pregnant group were higher.

If we analyse the tendencies by all subjective and objective measures, we see that pregnant women spent more time and energy expenditure with recreational type- or with vigorous activities, which refers to exercise. In contrast, in the non-pregnant group cumulative values of PA were higher, but in relation with work or in total, we assume that this alone did not have a positive effect. Type and intensity of PA seems to be significant.

Consistent with previous results, if the pre-treatment PA measures undergoing IVF/ICSI were analysed by secondary outcomes, correlations can only be found with time spent with recreation. Significant relationship was found with the number of retrieved oocytes ($R=0.315$, $p=0.045$), number of matured oocytes ($R=0.339$, $p=0.030$) and tendency-like relationship with Grade 1 embryos ($R=0.294$, $p=0.062$) by women who reached at least 150 minutes RPA measured by GPAQ-H.

Multivariate linear regression analysis

To define predicting factors of primary and secondary outcomes of IVF from pre-treatment habitual PA, psycho-socio-demographic variables, and baseline biomedical variables, we conducted a multivariate linear regression using the stepwise method.

We applied 3 models which included women's age, education, BMI, child-wish, duration of infertility and number of cycles, QoL and PSD parameters and PA values as covariates. In the first step, we adjusted for age, education, and BMI. In the second step, child-wish, duration of infertility and number of cycles were additionally adjusted. In the third step, we adjusted subscales of WHOQOL-BREF, FertiQoL, BDI, and FPI as well, and finally, in the fourth step PA parameters as IPAQ-SFH, GPAQ-H and ActiGraph data were also included.

In Model 1 ($R^2=0.367$) the number of oocytes, as the dependent variable was influenced positively by the GPAQ-H recreation MET ($F=10.994$, $p=0.004$; $B=0.005$, $p=0.004$, $B\text{ Constant}=4.604$).

The number of Grade 1 embryos was also examined as a dependent variable in Model 2 ($R^2=0.757$, $F=17.692$, $p<0.001$, $B\text{ Constant}=1.342$). Positive significant relationship was found with GPAQ-H recreational physical activity MET ($B=0.004$, $p<0.001$) and negative relationship with IPAQ sitting time ($B=-0.001$, $p\leq 0.001$) and BMI ($B=-0.167$, $p=0.038$).

When hCG levels on day 12 were considered as dependent variable, multivariate linear regression disclosed in Model 3 ($R^2=0.958$, $F=408.479$, $p<0.001$) that higher Very Vigorous Activity level measured with ActiGraph was accompanied with higher hCG levels ($B=63.703$, $p\leq 0.001$).

Logistic regression analysis

On the basis of biomedical, psycho-socio-demographic and PA variables, logistic regression analysis was conducted to evaluate the effects of all the above parameters on livebirths. Contrary to our previous findings, the results indicated that time (min/week) spent with moderate PA

measured with GPAQ (beta coefficient [B] = 0.002, standard error [SE] = 0.001, Wald = 3.944, p = 0.047, OR = 1.002) significantly associated with livebirths.

Discussion of key findings

It was assumed that the abundance of pre-treatment PA will increase general and infertility related QoL and decrease psychosocial distress domains in ART patients and thereby enhance reproductive performance. To assess the effects of psychosocial and lifestyle factors with special regard to physical activity on course and success of ART an observational cohort study was conducted with a follow-up of primary and secondary outcomes.

In relation to general QoL, in our study positive correlation was found between WHOQOL-BREF Psychological Domain and recreational activities. Positive relationship was described between more domains of the Core Scale of FertiQoL and Total MET, and also between Treatment Scale's Tolerability Subscale and MET of active transportation. Relationship between general PSD, measured with BDI and PA patterns cannot be described. Our results revealed by GPAQ-H, that recreational PA could counteract with some aspects of infertility related distress, RPA negatively correlated with Social Concern and Relationship Concern of FPI. Significant differences cannot be described using PAGA PA categories or the 240 minutes cut off point regarding QoL or PSD.

Regarding the examination of PA patterns, PAQs routinely overestimated all types and intensity of PA, but showed relatively good correlation with objective values. Self-reported time spent sedentary was strongly correlated with questionnaires and accelerometer measures. Cumulative values of PA in average were analogous to the Hungarian general population, but medians demonstrated that most of these women completely avoided vigorous forms of PA and showed pre-treatment PA patterns like women during pregnancy.

60.00% reported notable leisure time PA, and only 40.00% reached the recommended level of 150 min/week recreational moderate physical activity. They spend 16.98 hours per week with all forms of activity and spent 6.53 hours per day sedentary. 50.00% of the women in the sample reported regular exercise, which could be discussed as a relatively active subpopulation in Hungary compared to previous national studies [Bácsné et al. 2018, Gabnai et al. 2019]. However, Ács et al reported 10% improvement in PA habits based on representative Eurobarometer data from 2018: Hungarians' regular sport participation and physical activity is 33%, which is below the EU average (40%). Authors noted that 42% of Hungarian citizens spent more than 2.5 and less than 5.5 hours sedentary. With 6.53 hours daily sitting time (2745.17 ± 1755.39 min/day), our results are slightly elevated but are in line with the above findings [Ács et al. 2018].

Women were divided as per the abundance of clinical pregnancy. Pregnant women spent more time and energy expenditure with recreational type- or with vigorous activities, which refers to exercise. In contrast, in the non-pregnant group cumulative values of PA were higher, but in relation with work or in total, we assume that this alone did not have a positive effect. Type and intensity of PA seems to be significant. Significant relationship could be described with the number of retrieved oocytes, number of matured oocytes and tendency-like relationship with Grade 1 embryos by women who reached at least 150 minutes RPA measured by GPAQ-H.

Regarding GPAQ, our respondents performed moderate intensity PA during work and preferred that during recreation. However, mean values showed some vigorous activity in work (158.00 ± 467.34 min/week) and recreation (35.00 ± 82.70 min/week). Medians demonstrated that

most of these women completely avoided heavy forms of movement. Regarding female reproduction, there is a wide consensus on the beneficial effects of PA on gestation. Most studies draw attention to the risk of frequent vigorous PA on fertility [Green et al. 1986, Wise et al. 2012] and on success of ART [Morris et al. 2006, Domar et al. 2012].

To describe PA levels, both instrumental and self-reported studies were published. Evenson et al discussed that the adjusted odds of intrauterine gestation are higher among IVF patients who had higher continuous active living (OR 1.96, 95% CI 1.09–3.50), sports/exercise (OR 1.48, CI 1.02–2.15), and total activity (OR 1.52, 95% CI 1.15–2.01) indices in the past year [Evenson et al. 2014].

Regarding 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 compared to controls [Moran et al. 2011].

Palomba et al in their observational cohort study assessed the relationship between RPA and reproductive performance in connection with lifestyle interventions in obese infertile women who received ART (N=216). Number of pregnancies (16/41, 39.0% versus 28/175, 16.0%, respectively; $p=0.002$) and live births (10/41, 24.4% versus 13/175, 7.4%, respectively; $p=0.004$) were significantly higher in 41 obese patients who did regular physical activity compared to 175 obese controls who did not. After adjusting for confounders, the relative risks for a clinical pregnancy and livebirth were 3.22 (95% CI 1.53–6.78; $P=0.002$) and 3.71 (95% CI 1.51–9.11; $P=0.004$) in active patients, and RPA significantly correlated with improved reproductive performance irrespective of bodyweight loss [131]. In our study we found significant difference between pregnant and non-pregnant groups by GPAQ-H recreational PA MET means ($p=0.048$), which underline the importance of leisure time activities (inter alia) against PA in general.

On the other hand, adverse effects of excessive PA are also demonstrated. Gudmundsdottir et al. found that women who are active on most days, tended to experience fertility problems 3.2 times more often. In this study exercising to exhaustion also led to 2.3 times more fertility impairments than low intensity PA [Gudmundsdottir et al. 2009]. Based on the data by Morris et al. on lifetime exercise (level of evidence: II-2), exercising 4 hours or more per week indicate 40% less likelihood of having a livebirth (OR 0.6, CI 0.4-0.8), it is 3 times more likely to lead to cycle cancellation, and 2 times more likely to lead to implantation failure or pregnancy loss (OR 2.8, CI 1.5-5.3; OR 2.0, CI 1.4-3.1; OR 2.0, CI 1.2-3.4 respectively) compared to non-exercise [Morris et al. 2006]. In the current research during the follow-up of IVF outcomes, particular attention was given to the women in our sample who reported at least 4 hours PA weekly (18.2%). In our study neither negative nor positive effects can be concluded by exceeding 240 or even 300 minutes of activity per week. Significant relationship could be described in relation to reproductive performance (number of retrieved oocytes and number of matured oocytes) by women who reached at least 150 minutes pre-treatment RPA measured by GPAQ-H.

Espinós et al. reported in their meta-analyses based on 8 RCTs, that although lifestyle programmes improved pregnancy rates (RR: 1.43, CI: 95% 1.02 to 2.01; $I^2=60\%$; 8 RCTs; $N=1098$), they had no impact on live births (RR: 1.39, CI: 95% 0.90 to 2.14; $I^2=64\%$; 7 RCTs; $N=1034$) and increased risk of miscarriage in obese infertile women [Espinós et al. 2020]. In our sample positive association was found between moderate PA and live births and no relationship with the ratio of miscarriage.

An analysis of 121 744 women with failed first treatment revealed that female age is a key predictor of failure to have a livebirth following IVF as well as the risk of hindered performance, while increased duration of infertility is also associated with poorer outcomes at every stage [Bhattacharya et al. 2013]. Comparing these results to our models, we cannot confirm the emphasized importance of age on reproductive performance.

To define predicting factors of primary and secondary outcomes of IVF from the point of view of PA, QoL and PSD, we conducted a multivariate linear regression using the stepwise method. We applied 3 models, which included women's age, education, BMI, child-wish, duration of infertility and number of cycles, QoL and PSD parameters, and PA values as covariates. In Model 1 the number of oocytes was influenced positively by the GPAQ-H recreation MET, in Model 2 the number of Grade 1 embryos was positively correlated with GPAQ-H recreational physical activity MET and negatively with IPAQ sitting time and BMI. It was disclosed in Model 3 that higher Very Vigorous Activity level measured with ActiGraph was accompanied by higher hCG levels.

Gaskins and co-authors reported similar findings on maternal PA and sedentary behaviour in relation to ART's reproductive outcomes. They found no association between MVPA time or total MET and outcomes as probability of implantation, clinical pregnancy or live birth. However, specific leisure time activities (aerobics, rowing, exercising with ski or stair machine) were positively associated with live birth (p-trend=0.02) [Gaskins et al. 2016].

Conclusions

Infertility-specific provide more appropriate information on QoL and distress of ART patients. GPAQ-H could be used as a valid measurement tool for mapping PA habits of ART patients. Based on our results, recreation type of pre-treatment PA could positively influence domains of infertility related QoL and PSD during ART and improve reproductive performance. Existing differences in response to infertility due to PA suggest the need for development of a specific intervention.

Limitations

The limitations of the study include the sample's non-representative nature. To avoid potential confounders, patients were carefully selected, but made the study population modest. Objective measurement of PA patterns cannot be conducted by all patients and complete medical record was also missing in a portion of patients.

A post-hoc sample size estimation (using G*Power for Mac version 3.1.9.6) for the multivariate linear regression analysis (significance set at 5%, power set at 0.8, effects size at 0.15, and number of predictors at 2) showed that a total of 55 subjects would have been required to ensure adequate statistical power for analyses. The final sample of 45 subjects did not meet the sample requirements. Whereas the sample size was relatively suboptimal, given the limited study power, i.e 71.84%, to detect the difference in primary and secondary outcomes of ART.

For more impressive results on the effects of physical activity on the effectiveness of fertility programmes, a detailed objective assessment of physical activity, increased number of participants, and further examinations on outcome measures, with live birth's rate as end point are needed in a well-powered randomized controlled prospective study.

Clinical implication

Infertility-specific and general scales could provide appropriate information on QoL and PSD of ART patients. Pre-treatment PA may positively influence domains of QoL and PSD during ART and reproductive performance.

Therefore, combined investigation of these factors is recommended to identify patients who could benefit from psychosocial interventions or lifestyle changes. After more detailed Randomized controlled trial (RCT)-based examinations, a routine screening protocol of ART patients can be developed for psychosocial and lifestyle screening. For promoting appropriate pre-treatment PA habits, development of a specific guideline for ART patients is recommended.

Recruiting patients in intervention groups, offering exercise sessions and facilitation to perform the needed RPA under the guidance of health professionals could be also favourable. These groups could also act as peer support groups, raising the positive effects of PA interventions with psychosocial benefits and would provide protection against medicalization. Exploration of patient experiences during ART could also help offset negative reactions to infertility and its treatment, to improve willingness to continue with the treatment, may improve patient outcomes, and, if the treatment is unsuccessful, may support to cope with the circumstances of remaining childless.

Parallel to the psychosocial support, a multi-centre study with the University of Novisad and the Karolinska Institutet on insulin resistance, physical activity and ART is under preparation.

Summary of novel findings

1. Longitudinal analyses of the utilization of assisted reproductive treatments based on International Classification of Health Interventions (WHO) codes in Hungary between 2010-2018 on the National Health Insurance Fund's dataset demonstrated the changing patterns and the importance of fertility interventions in Hungary. 61.39% expansion in the cumulative number of cases and 2.122 years increase in the mean age of patients, robust regional and territorial differences by NUTS 1 regions and by counties could be described.
2. Based on a cross-sectional, observational cohort pilot study, it was assumed that infertility-specific scales provide more appropriate description on mental status of ART patients than general scales and abundance of regular pre-treatment physical activity may increase the success rate of ART measured by clinical pregnancy.
3. To the best of our knowledge the main study of the thesis was the first in Hungary which gave a detailed description on the physical activity patterns of the specific cohort of patients undergoing assisted reproductive treatment using ActriGraph GT3X accelerometers, IPAQ-SF and GPAQ-H questionnaires. The study also presented the relationship between PA patterns and psycho-socio-demographic characteristics or primary and secondary outcomes of ART.
4. The ActiGraph GT3X and GPAQ-H can be used as valid measurement tools to map the PA habits of ART participants. Noting that the definite difference between objective and subjective assessment of PA highlights the need to improve Physical Literacy of women undergoing AR
5. Based on our results, pre-treatment recreational-type PA may positively affect infertility-related QoL and PSD areas during ART and improve reproductive potential relative to secondary outcome measures. Physical activity can have a positive effect on live births.
6. Existing differences in response to infertility due to PA suggest the need for the development of a specific intervention.

Acknowledgements

First of all, I am greatly indebted to my supervisors, Dr Ákos Várnagy and Dr Kinga Lampek for their invaluable help and advice during my doctoral research.

I am grateful to the Doctoral School of Health Sciences, first of all to Prof Dr József Bódis, the Head of the Doctoral School, to Prof Dr Endre Sulyok, Secretary of the Doctoral School of Health Sciences, and to Prof Dr Ildikó Kriszbacher†, former Secretary of the Doctoral School.

I am also grateful to the leaders of the Faculty of Health Sciences, especially to Dr habil András Oláh and Prof Dr Pongrác Ács for providing the opportunity for performing my scientific work besides my professional duties.

I would like to express my gratitude for all research and publication experience I gained in the frame of the MTA-PTE Human Reproduction Scientific Research Group.

Dr Alexandra Makai, Kata Füge, Dr BIBI Vahideh Moghaddam Hosseini, Dr Ágnes Nagy, Dr Jill Taube, Dr Anna Duberg, Prof Dr Margareta Moeller, Dr Márta Szalai, Dr Boróka Gács and Róbert Pónusz inspired me through their professional and personal help and example, guiding me in finding my research scope and supporting me during my work, which is gratefully acknowledged.

I would also like to thank Prof. Dr. Miklós Koppán as the current Director and Prof. Dr. József Bódis as the previous Director of the Department of Obstetrics and Gynaecology, University of Pécs. I appreciate all health professionals especially Krisztina Gödöny and Grimné Locskai Elvira at the Assisted Reproduction Unit, Department of Obstetrics and Gynaecology for their great cooperation.

I also wish to thank the women who underwent ART for participating in the study at such a challenging time in their life.

Finally, my heartfelt thanks to my family, my husband, Norbert and my daughters, Blanka and Luca for their support, patience and tolerance over the past years.

Metrics

Full texts: 42, Abstracts: 50
Number of SJR articles: Q1 - 5, Q2 - 6, Q3-1
IF: 24.812
Citations (without self-citations): 40
H-index: 4

ORCID: [0000-0002-4059-104X](https://orcid.org/0000-0002-4059-104X)

Scopus ID: [56344311800](https://scopus.com/authid/detail.uri?https://orcid.org/0000-0002-4059-104X)

Web of Science Researcher ID: [AAR-8604-2020](https://orcid.org/0000-0002-4059-104X)

Publons ID: <https://publons.com/researcher/3731007/viktoria-premusz/>

ResearchGate: [Viktoria Premusz](https://www.researchgate.net/profile/Viktoria_Premusz)

RG Score 23.75

http://www.researchgate.net/profile/Viktoria_Premusz

List of Publications

In extenso publications

Articles related to the thesis

Prémusz, V; Makai, A ; Perjés, B ; Máté, O ; Hock, M ; Ács, P ; Koppán, M ; Bódis J ; Várnagy, Á[#] ; Lampek, K^{#húá}. (# equally contributed)

Multicausal analyses on psychosocial and lifestyle factors undergoing assisted reproductive therapy – with special regard to self-reported and objective measures of pre-treatment habitual physical activity. BMC PUBLIC HEALTH S20, pp. 1-13. (2020)

In Press, IF 2.521

Ács, P ; Betlehem, J ; Oláh, A ; Bergier, B ; Morvay-Sey, K ; Makai, A ; **Prémusz, V**. Cross-cultural adaptation and validation of the Global Physical Activity Questionnaire among healthy Hungarian adults. BMC PUBLIC HEALTH pp. 1-11. DOI : 10.1186/s12889-020-08477-z (2020)
In Press, IF 2.521

Prémusz, V ; Makai, A ; Gács, B ; Nagy, Á ; Perjés, B ; Ács, P ; Lampek, K ; Várnagy, Á .

Preliminary study on pre-treatment physical activity and quality of life in infertility
EXERCISE AND QUALITY OF LIFE: JOURNAL OF SCIENCE IN SPORTS 11 : 2 pp. 5-17. ,
12 p. (2019)

Prémusz, V; Makai, A; Nagy, Á; Perjés, Betarix ; Ács, Pongrác ; Lampek, Kinga ; Várnagy, Á .
Sisztematikus irodalmi áttekintés kvalitatív szintézise a fizikai aktivitás méréséről az asszisztált reprodukcióval összefüggésben

SPORT- ÉS EGÉSZSÉGTUDOMÁNYI FÜZETEK 3 : 4 pp. 1-13. (2019)

Prémusz, V ; Makai, A ; Gács, B ; Simon-Ugron, Á ; Ács, P ; Lampek, K ; Várnagy, Á .

Relationship between pre-treatment habitual physical activity and success of assisted reproduction
STUDIA UNIVERSITATIS BABES-BOLYAI EDUCATIO ARTIS GYMNASITICAE 58 : 3 pp.
41-58. (2018)

Prémusz, V ; Makai, A ; Melczer, C ; Perjés, B ; Ács, P ; Bódis, J ; Lampek, K ; Várnagy, Á .

Habitual fizikai aktivitás és életminőség összefüggése várandósság alatt a WHO Global Physical Activity Questionnaire alapján

MAGYAR NŐORVOSOK LAPJA 81 : 6 pp. 343-350. (2018)

Additional articles

Ács, P ; Betlehem, J ; Oláh, A ; Bergier†, J ; Melczer, Cs ; **Prémusz, V**[#] ; Alexandra Makai[#] .(#
equally contributed)

Measurement of public health benefits of physical activity: Validity and reliability study of the International Physical Activity Questionnaire in Hungary.

BMC PUBLIC HEALTH, DOI : 10.1186/s12889-020-08508-9 pp. 1-12. (2020)

In Press, IF 2.521

Rétsági, E ; **Prémusz, V** ; Makai, A ; Melczer, Cs ; Betlehem, J ; Lampek, K ; Ács, P ; Hock, M.
Association with subjective measured physical activity (GPAQ) and quality of life (WHOQoL-
BREF) of ageing adults in Hungary, a cross-sectional study

BMC PUBLIC HEALTH DOI: 10.1186/s12889-020-08833-z, pp. 1-10. (2020)

In Press, IF 2.521

Bódis, J ; Sulyok, E ; Kőszegi, T ; **Prémusz, V** ; Várnagy, Á ; Koppán, M .

Serum and follicular fluid levels of serotonin, kisspeptin, and brain-derived neurotrophic factor in patients undergoing in vitro fertilization : an observational study: Neurohormones in patients receiving IVF

JOURNAL OF INTERNATIONAL MEDICAL RESEARCH UNSP 0300060519879330

<https://doi.org/10.1177/0300060519879330> pp 1-15. (2020) IF 1.287

Bódis, J ; Sulyok, E ; Kőszegi, T ; Gödöny, K ; **Prémusz, V** ; Várnagy, Á .

Serum and follicular fluid levels of sirtuin 1, sirtuin 6, and resveratrol in women undergoing in vitro fertilization: an observational, clinical study.

JOURNAL OF INTERNATIONAL MEDICAL RESEARCH 47 : 2 pp. 772-782. (2019) IF 1.287

Melczer, Cs ; Melczer, L ; Raposa, BL ; **Prémusz, V** ; Makai, A ; Ács, P .

Assesment the physical activity of heart failure patients by telemetry data

SPORT- ÉS EGÉSZSÉGTUDOMÁNYI FÜZETEK 3 : 3 pp. 25-38. (2019)

Nagy, AL ; **Prémusz, V** ; Beatrix, Perjés ; Anna, Duberg ; Gabriella, Hegyi

Dance as Moderate Intensity Activity in the Stress Management among Teenage Girls

HEALTH EDUCATION AND PUBLIC HEALTH 2 : 2 pp. 181-186. (2019)

Moghaddam Hosseini, V ; Makai, A ; Varga, K ; Ács, P ; **Prémusz, V** ; Várnagy, Á .

Assessing fear of childbirth and its predictors among Hungarian pregnant women using Wijma Delivery Expectancy/Experience Questionnaire subscales

PSYCHOLOGY HEALTH & MEDICINE 24 : 7 pp. 879-889. (2019) IF 1.706

Várnagy, Á ; Kőszegi, T ; Györgyi, E ; Szegedi, S ; Sulyok, E ; **Prémusz, V** ; Bódis, J .

Levels of total antioxidant capacity and 8-hydroxy-2'-deoxyguanosine of serum and follicular fluid in women undergoing in vitro fertilization: focusing on endometriosis.

HUMAN FERTILITY pp. 1-9 (2019) IF 2.161

Ács, P ; **Prémusz, V** ; Melczer, Cs ; Bergier, J ; Salonna, F ; Junger, J ; Makai, A .

Nemek közötti különbségek vizsgálata a fizikai aktivitás vonatkozásában a V4 országok egyetemista populációjának körében

MAGYAR SPORTTUDOMÁNYI SZEMLE 19 : 74 pp. 3-9. (2018)

External citations: 2, Self citations: 0, Unhandled citations: 0, All citations: 2

Ács, P ; **Prémusz, V** ; Morvay-Sey, K ; Kovács, A ; Makai, A ; Elbert, G .

A sporttal, testmozgással összefüggésben lévő mutatók változása Magyarországon és az Európai Unióban az elmúlt évek eredményeinek nyomán

SPORT- ÉS EGÉSZSÉGTUDOMÁNYI FÜZETEK 2 : 1 pp. 61-76. (2018)

Makai, A ; **Prémusz, V** ; Lampek, K ; Ács, P ; Simon-Ugron, Á ; Figler, M .

Sitting Time and Sport Participation of the Employed Population In Hungary and Europe

STUDIA UNIVERSITATIS BABES-BOLYAI EDUCATIO ARTIS GYMNASITICAE LVIII : 2 pp. 11-22. (2018)

Makai, A ; **Prémusz, V** ; Ács, P ; Figler, M

Fizikai aktivitás mértékének vizsgálata a magyarországi munkavállalók körében egy európai keresztmetszeti vizsgálat alapján

SPORT- ÉS EGÉSZSÉGTUDOMÁNYI FÜZETEK 2 : 2 pp. 3-16. (2018)

Bánkyné, PB ; **Prémusz, V** ; Nagy, Á ; Várnagy, Á ; Bódis, J .

Szülésfelkészítő tréning?: A várandósság alatt végzett rendszeres testedzés hatása a szülés kimenetelére – Irodalmi áttekintés

SPORT- ÉS EGÉSZSÉGTUDOMÁNYI FÜZETEK 1 : 2 pp. 3-17. (2017)

Szalai, M ; Szirmai, A ; Füge, K ; Makai, A ; Erdelyi, G ; **Premusz, V[#]** ; Bodis, J[#] .

Special aspects of social support: Qualitative analysis of oncologic rehabilitation through a belly dancing peer support group.

EUROPEAN JOURNAL OF CANCER CARE 26 : 6 Paper: e12656 , 14 p. (2017) IF 2.409,

External citations: 3, All citations: 3

Makai, A ; **Prémusz, V** ; Füge, K ; Figler, M ; Lampek, K .

Social Participation and Health among Ageing People in East-Central Europe

PRACTICE AND THEORY IN SYSTEMS OF EDUCATION 10 : 2 pp. 177-185. , 9 p. (2015)

External citations: 1, All citations: 1

Szalai, M ; Levay, B ; Szirmai, A ; Papp, I ; **Premusz, V** ; Bodis, J .

A Clinical Study to Assess the Efficacy of Belly Dancing As a Tool for Rehabilitation in Female Patients with Malignancies.

EUROPEAN JOURNAL OF ONCOLOGY NURSING 19 : 1 pp. 60-65. (2015) IF 1.618

External citations: 9, All citations: 10

Makai, A ; **Prémusz, V** ; Figler, M ; Lampek, K .

Az idősödő népesség szubjektív életminősége és társas aktivitása

In: Ács, Pongrácz (eds.) Tudományos szemelvények a Pécsi Tudományegyetem Egészségtudományi Kar Fizioerápiás és Sporttudományi Intézetének jelenéből : Jubileumi tanulmánykötet Kránicz János 70. születésnapja alkalmából

Pécs, Hungary : Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), pp. 78-86. (2014)

Szalai, M ; Rektorovics, K R ; **Prémusz, V** .

Orientalis tánc, mint rehabilitációs módszer a rosszindulatú daganatos megbetegedésekben

NŐVÉR 27 : 1 pp. 26-34. , 9 p. (2014)

External citations: 1, All citations: 1