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Effect of energy expenditure and physical activity on the outcomes of assisted reproduction treatment


Mert Kucuk ^{a,*}, Fadime Doymaz ^b, Bulent Urman ^a

^a Assisted Reproduction Unit of the Vehbi Koc Foundation American Hospital, Guzelbahce, Sokak no. 20 Nisantasi 34365, Istanbul, Turkey; ^b Hacettepe University Faculty of Health Science, Department of Physical Therapy and Rehabilitation, Ankara, Turkey

* Corresponding author. E-mail address: dr.mertkucuk@gmail.com (M Kucuk).



Mert Kucuk received his medical degree from the Hacettepe School of Medicine in 1999. He completed his Obstetrics and Gynecology residency training in the Adnan Menderes University School of Medicine. Following a certification program in infertility and assisted reproduction at the Vehbi Koc Foundation American Hospital, he is currently attending a certification program on intracytoplasmic sperm injection within the same institution. His major areas of interest are reproductive endocrinology, clinical infertility and assisted reproduction.

Abstract It is still not definitely resolved whether being physically active has any impact on the success of assisted reproduction treatment. To this end, this study used the International Physical Activity Questionnaire short form (IPAQ-sf). Data from the IPAQ-sf were classified into three categories: low, moderate and high physical activity as defined by the IPAQ working group. The subjects in the study were grouped according to their physical activity levels during treatment. None of the subjects met the criteria for high physical activity. The low activity group consisted of 68 women whereas moderate activity group consisted of 63 women. The study showed that women undergoing assisted reproduction treatment significantly decreased their activity level during the treatment period ($P < 0.05$). However, women who were physically more active were more likely to have an increased implantation rate and a live birth. 

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Introduction

The major determinants of success in assisted reproduction are female age and the presence of good-quality embryos available for transfer. Numerous other factors may have an impact, one being the level of physical activity during the treatment period. Whether being physically active compared with the adoption of a more sedentary lifestyle during

treatment affects pregnancy and live birth rates is not known. There are studies in the literature that compared the outcome of treatment in women advised to have bed rest after embryo transfer as opposed to liberal physical activity, all of which showed no benefit of the former strategy (Amarin and Obeidat, 2004; Bar-Hava et al., 2005; Botta and Grudzinskas, 1997; Purcell et al., 2007; Sharif et al., 1995, 1998). However, in all of these studies, the effect

on pregnancy rates of brief (20–60 min) or a relatively more prolonged bed rest (up to 24 h) after embryo transfer was studied. In all these studies, the authors seem to be satisfied and were content with only stating 'no worse results after no bed rest' or limiting physical activity after embryo transfer. However, the data needs to be extended further to question if limiting physical activity during treatment has a negative effect on the outcome by using a standard and reliable tool that assesses physical activity of the subjects objectively and for a longer duration both before and during the treatment.

In a postal survey performed among IVF unit directors in Australia and New Zealand, prolonged bed rest following embryo transfer was voted as a more important factor that may influence the treatment outcome than a trial transfer or ultrasound monitoring of the embryo transfer procedure (Kovacs, 1999). This opinion seems to be shared by the patients as well. However, patient preferences regarding physical activity before and during treatment have not been studied and quantified in detail, although it is plausible that a voluntary decline in physical activity is likely (Su et al., 2001).

The aim of this study was to quantify physical activity and energy expenditure before and during assisted reproduction treatment and to correlate these variables with implantation and live birth rates.

Materials and methods

The study was undertaken in the Assisted Reproduction Unit of Vehbi Koc Foundation (VKF) American Hospital between June 2007 and October 2007. All women undergoing their first fresh non-donor treatment cycle were offered to participate in the study. Participation was on a voluntary basis. The study was approved by the institutional review board and informed consent was obtained from all participants. None received pretreatment counselling regarding the impact of being physically active on the outcome of assisted reproduction treatment as this was not routine procedure in the study clinic at the time the study was initiated. All patients were advised at the time of embryo transfer to lead their normal lives and not to limit their physical activity. Women undergoing treatment ($n = 131$) completed the survey assessing their general physical characteristics, infertility and ovarian stimulation protocols.

Ovarian stimulation was mostly performed with a long gonadotrophin releasing hormone agonist protocol combined with recombinant human FSH (Gonal-F; Serono, Bari, Italy). The ovarian stimulation treatment was individualized and adjusted according to the response. Final maturation of the oocytes was induced with 10 000 IU human chorionic gonadotrophin (Pregnyl; Organon, Istanbul, Turkey) which was administered intramuscularly when the leading follicle reached 20 mm in the mean diameter and was accompanied by two follicles of >16 mm. Oocyte retrieval was performed 36 h later. Intracytoplasmic sperm injection was performed according to conventional protocols to fertilize the oocytes. Up to three embryos were transferred vaginally. The luteal phase was supported with 90 mg vaginal progesterone gel (Crinone 8%; Serono, Bedfordshire, UK) starting from the day of oocyte collection until the day the pregnancy test

was performed. Vaginal progesterone gel was continued in women with a positive pregnancy test until the 12th week of gestation.

A clinical pregnancy was defined as the presence of a gestational sac on vaginal ultrasound examination performed at the sixth week of gestation. Implantation rate was calculated separately for each woman as number of gestational sacs divided by number of transferred embryos multiplied by 100.

IPAQ-sf and energy expenditure

Use of a standardized questionnaire to assess physical activity is very important. The International Physical Activity Questionnaire (IPAQ-sf) was used to evaluate activity levels and energy expenditure of the participants before and during the treatment period. The questionnaire was administered by an interviewer. IPAQ-sf is easily available on the internet (International Physical Activity Questionnaire, 2001).

The IPAQ-sf was used to evaluate walking time and moderate and vigorous activities. The scale questions assessing activity levels of the subjects during treatment include questions such as, 'In the last 7 days, how many days did you spend doing moderate activities?' and 'How much time did you usually spend on one of those days doing moderate physical activities?' (Craig et al., 2003). On the other hand, in order to evaluate the activity levels among the subjects prior to assisted reproduction treatment, the questionnaire contained questions such as 'In a usual 7-day period before the assisted reproduction treatment, how many days did you spend performing moderate activities?' and 'How much time did you usually spend on one of those days performing moderate activities?' Frequency of activity is measured in days and duration in hours and minutes. The questions aiming to assess activity levels and energy expenditure of the subjects during treatment were given 7 days after embryo transfer (before the pregnancy test), while activity levels and energy expenditure of the subjects before treatment were questioned before the initiation of the treatment cycle.

Metabolic equivalent (MET) is defined as the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 kcal (4.184 kJ)/kg/h: 1 MET denotes the energy cost of sitting quietly. MET levels were taken from the 2000 Compendium of Physical Activities (Ainsworth et al., 2000). The compendium offers a coding scheme for specific activities performed in various settings. Their respective MET intensity levels are provided to score physical activity questionnaires and to facilitate consistency (Ainsworth et al., 2000; Conway et al., 2002). All types of walking, moderate-intensity and vigorous-intensity activity were included to the related category to create an average MET value. Time variables lower than 10 min/day were recoded to zero. As specified by the IPAQ executive committee, the minutes per week during which vigorous, moderate and walking activity were performed were multiplied by a factor of 8, 4 or 3.3, respectively (Tehard et al., 2005). The total physical activity (MET-min/week) was assessed by the sum of walking, moderate and vigorous MET-minutes (Craig et al., 2003; International Physical Activity Questionnaire, 2001).

IPAQ-sf and physical activity

Data from the IPAQ-sf were recoded in a categorical score and classified into three categories, low, moderate and high physical activity, as defined by the IPAQ working group (www.ipaq.ki.se/scoring.htm). Participants were included in the moderate activity group if they performed a minimum of 5 days of any combination of walking, moderate or vigorous activity accumulating a total of at least 600 MET-min/week or a minimum of 3 days of vigorous activity of at least 20 min per day or a minimum of 5 days of moderate-intensity activity or walking of at least 30 min per day. Participants were included in the high activity group if they performed a minimum of 7 days of any combination of walking, moderate or vigorous activity accumulating a total of at least 3000 MET-min/week or vigorous activity on a minimum of 3 days accumulating at least 1500 MET-min/week. Subjects who did not meet the criteria for moderate or high activity group were grouped as low activity group as described in the IPAQ guidelines (*International Physical Activity Questionnaire, 2005*).

Statistical analyses

Data were presented as means \pm standard deviation. MET-minutes/week were presented as median values. It was observed that physical activity scores were strongly skewed and standard deviations were two times the mean scores, as the previous research and datasets with physical activity self-reports revealed (*Tehard et al., 2005*). Parametric continuous variables were analysed by *t*-test and nonparametric data were analysed by using the Mann–Whitney *U*-test. Differences between categorical variables were analysed by chi-squared test. Wilcoxon matched-pairs signed-rank sum test was used for the comparison of energy expenditure of the subjects before and during treatment. The correlation

analyses were performed with Spearman correlation test. The statistical analysis was carried out using the Statistical Package for Social Sciences version 13.0. Significance was defined as $P < 0.05$.

Results

A total of 131 subjects agreed to participate in the study. The subjects in the study were grouped according to their activity level during treatment. No subject met the high activity group criteria during treatment so the study was performed with low and moderate activity groups. The low activity group consisted of 68 women whereas the moderate activity group consisted of 63 women. Both groups were comparable for age, body mass index, ovarian stimulation protocol applied, oocytes retrieved, oocytes fertilized and the mean number of embryos transferred (**Table 1**).

When all the subjects were evaluated, implantation rate was 24.4% and percentage of retrievals resulting in live births was 34.4%. Women in the moderate activity group who were more physically active during treatment had an increased live birth rate per retrieval (moderate activity 47.6% versus low activity 22.1%) and implantation rate (moderate activity 29.6% versus low activity 19.4%) compared with low activity group ($P < 0.05$) (**Table 1**).

A significant positive correlation was found between live birth results and the energy expenditure ($r = 0.23$, $P < 0.05$) and physical activity level of the subjects ($r = 0.27$, $P < 0.05$) during treatment. However, such a correlation was not found for live birth results of the subjects and their energy expenditure and activity levels prior to treatment.

Figure 1 shows the number of subjects according to physical activity groups prior to and during treatment. For the high activity group, 15 subjects met the criteria prior to treatment and no subject met the criteria during treatment. For the moderate activity group, 99 subjects met

Table 1 Patient characteristics and outcome of assisted reproduction treatment in the two study groups.

	Low activity group (n = 68)	Moderate activity group (n = 63)	P-value
Patient age (years)	33.5 \pm 5.2	33.9 \pm 5.1	NS
Transferred embryos	2.4 \pm 0.9	2.5 \pm 0.9	NS
Oocytes retrieved/patient	8.8 \pm 5.4	8.8 \pm 4.2	NS
Oocytes fertilized/patient	5.5 \pm 3.5	5.5 \pm 2.7	NS
Clinical pregnancy rate (%)	23/68 (33.8)	34/63 (54.0)	0.02
Implantation rate (%)	31/160 (19.4)	45/152 (29.6)	0.035
No. of retrievals resulting in a live birth (%)	15 (22.1)	30 (47.6)	0.002
BMI (kg/m ²)	24.7 \pm 4.7	24.7 \pm 3.9	NS
<i>No. of embryo transfers</i>			
Day 2	20	20	NS
Day 3	39	35	
Day \geq 4	9	8	
<i>No. of ovarian stimulation protocols (%)</i>			
Long protocol	46 (67.6)	41 (65.1)	NS
Antagonist protocol	19 (27.9%)	18 (28.6)	
Other protocols	3 (4.4)	4 (6.3)	

Values are means \pm SD unless otherwise stated; BMI = body mass index; NS = not statistically significant.

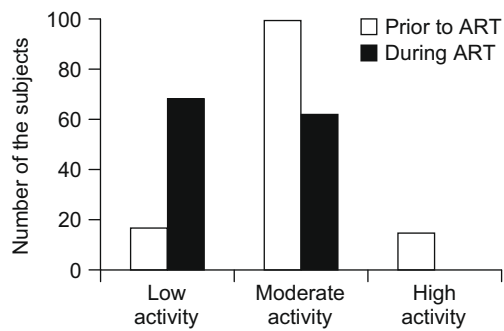


Figure 1 Number of subjects according to physical activity group prior to and during assisted reproduction treatment.

the criteria prior to treatment and 63 subjects met the criteria during treatment. For the low activity group, 17 subjects met the criteria prior to treatment and 68 subjects met the criteria during treatment.

There was no difference between the energy expenditure of the groups prior to assisted reproduction treatment (moderate activity 1782 MET-min/week versus low activity 1584 MET-min/week) (Table 2) (The subjects are grouped according to their activity levels during treatment). The study also observed that subjects undergoing treatment significantly decreased their activity level during treatment compared with their activity level prior to treatment (whole group prior to treatment 1782 MET-min/week versus during treatment 693 MET-min/week; $P < 0.05$) (Figure 2).

Discussion

This prospective clinical study addressed the question of whether physical activity and energy expenditure before and during treatment had any influence on implantation and live birth rates. As far as is known, there are only a few studies investigating the relationship between physical activity and outcome of assisted reproduction treatment (Su et al., 2001) and there appears to be no study evaluating the energy expenditure of the subjects undergoing assisted reproduction treatment.

Much of the research in the area has been based on a limited time of bed rest after embryo transfer. However physical activity levels and energy expenditure of the subjects during and prior to treatment and their effect on the outcomes have not been studied and quantified in detail. According to this study, infertile subjects undergoing assisted reproduction treatment significantly decreased their activity levels during treatment. The implantation and live

birth rates in this study are consistent with the previous data (Wright et al., 2008).

In the study by Bar-Hava et al. (2005), nearly 60% of the patients preferred being in the bed rest arm although they had been provided guidance about the lack of benefit of bed rest. Moreover, some patients are known to limit their physical activity until the day of the pregnancy test although they are not advised to do so by medical experts. Most patients even refrain from physical activity after positive pregnancy test results.

In their study, Su et al. (2001) reported that most subjects restricted their daily activities following IVF/embryo transfer. Of the 60 participants in their study, 56 reported that they rested in bed for more than 2 h following embryo transfer. As they reported, during the 2-week waiting period after embryo transfer, 55 walked at a slow pace, 51 limited their social activity, 47 avoided using stairs, 45 limited their self-care activity and 40 adjusted their work load. The authors did not evaluate the energy expenditure and physical activity status of the subjects.

This study found that women undergoing assisted reproduction treatment significantly decreased their activity level during the treatment period. These data are consistent with the results of Su et al. (2001). The study also found women who were physically more active during treatment had increased implantation rate and live birth rates. Consistent with the present data, Rezábek et al. (2001) also reported a negative effect of overnight rest after embryo transfer on IVF outcome, although in that study the numbers did not reach statistical significance.

It is possible that the results of the present study arise from the positive effects of physical activity on stress and anxiety reduction. The frequency of self-reported negative psycho-emotional experiences both before and during diagnosis and treatment was found higher among women facing fertility problems when compared with those without fertility problems (Oddens et al., 1999). It has been demonstrated that stress influences reproduction outcomes, such as the number of oocytes retrieved and fertilized, pregnancy and live birth rates (Klonoff-Cohen et al., 2001). Coping modes with anxiety and depression might affect the success of an assisted reproduction treatment procedure through hormonal or endorphin mediation (Merari et al., 1992). Serum prolactin and cortisol concentrations and state anxiety scores have been shown to increase during stimulated treatment cycles (Csemiczky et al., 2000; Harlow et al., 1996). As was demonstrated, prolonged periods of stress and anxiety were associated with high amounts of activated T cells in the peripheral blood. Furthermore, reduced implantation rates in women have also been

Table 2 Energy expenditure before and during assisted reproduction treatment.

Level of physical activity	Total energy expenditure (MET-min/week)		P-value
	Before treatment	During treatment	
Low	1584	189	0.001
Moderate	1782	1530	
High	3366	—	

Values are medians; MET = metabolic equivalent.

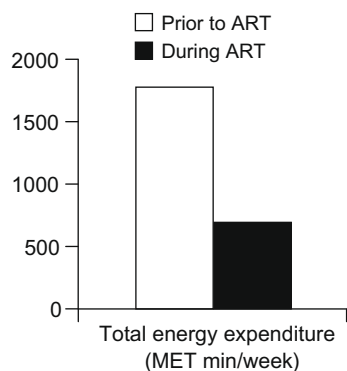


Figure 2 Total energy expenditure of the subjects prior to and during assisted reproduction treatment. MET = metabolic equivalent.

associated with such immunological changes in turn (Gallinelli et al., 2001). Furthermore, as speculated, maternal stress following embryo transfer decreases immediately when the subject goes back to routine daily activities (Orvieto et al., 1998). It is possible that patients preferring to be more physically active felt more confident and less stressed than those limiting their physical activity and that these positive feelings positively contributed to their chances of conception. Furthermore, anxiety and depression scores were found higher in women who had undergone treatment and did not achieve pregnancy than women who achieved pregnancy (Csemiczky et al., 2000; Kee et al., 2000; Koryntova et al., 2001).

Energy expenditure is a sensitive marker of physical activity status. This study has collected information about physical activity levels and energy expenditure of subjects during an IVF cycle, which are postulated to affect outcomes. This study is unique because the physical activity levels of the participants were evaluated and categorized with a standard reliable and an extensively validated international tool like the IPAQ (Craig et al., 2003; Maddison et al., 2007; Rangul et al., 2008). The energy expenditure of the subjects were evaluated as MET values, which yield very objective information on physical activity. The MET values obtained in this study are consistent with those reported by previous studies (Booth, 2000; Craig et al., 2003; Rangul et al., 2008). The short version of the questionnaire is more acceptable both to investigators and respondents and no difference was detected in terms of validity and reliability between the short and long versions of IPAQ (Craig et al., 2003). Thus, the short version was preferred for the present study. Interviewer administration was also preferred following the recommendations of the IPAQ working team to use face-to-face interviews in developing countries (Hallal et al., 2003).

There are some limitations to this study. The doubly labelled water (DLW) technique is considered the gold criterion measure of physical activity-related energy expenditure. However, DLW is expensive, time consuming and hard to perform (Maddison et al., 2007). Physical activity recall questionnaires may either under- or overestimate energy expenditure: for this aim, physical activity records may be more accurate (Conway et al., 2002). There may be inaccuracies in the self-reporting of physical activity, but IPAQ-sf data

was obtained before the knowledge of the cycle outcome. Inaccuracies should not be different in patients with low or moderate activity.

The results of this study should be interpreted with caution. These data cannot be generalized for vigorous activity since there was no subject fulfilling the criteria for vigorous activity during treatment. Also it should be kept in mind that the study was not planned to question the benefit of a brief period of bed rest after embryo transfer.

Most fertility centres advise some kind of restriction of physical activity in the patient's daily life after embryo transfer (Sharif et al., 1995). According to these results, this is unfounded, because better outcomes were recorded in women who were physically more active during assisted reproduction treatment and the period after embryo transfer.

In summary, it is concluded that women have a tendency to decrease their physical activity levels during assisted reproduction treatment. Subjects undergoing treatment significantly decreased their physical activity levels even though they were not advised to do so and there is a strong tendency, to negative effect, of limiting physical activity during treatment on outcome. The women who were physically more active during treatment were more likely to have increased implantation rates and live birth results. The authors suggest that clinicians should encourage patients to keep on their routine daily physical activity levels. To be able to conclude that increasing exercise is beneficial, a study needs subjects engaging in vigorous activity. Prospective randomized control studies should be performed to determine any impact of vigorous physical activity on treatment outcome.

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