URF PUBLISHERS
connect with research world

Medical & Clinical Case Reports Journal

Original Research

Physical Activity and Oocyte Maturation in Assisted Human Reproduction: A Prospective Study

Fatima Olaso[1]*, Rosario Mendoza[1], Iñaki Echeverria[2], Jon Irazusta[3] and Roberto Matorras[4]

[1]Obstetrics and Gynaecology Department. Human Reproduction Unit, Cruces University Hospital. Barakaldo, ESP

[2]Physical Education and Sports Department. University of the Basque Country. Leioa, ESP

[3]Physiology Department. University of the Basque Country. Leioa, ESP

[4]Obstetrics and Gynaecology Department. Human Reproduction Unit, Cruces University Hospital. Barakaldo, ESP. Reproductive Medicine. IVI Bilbao, IVIRMA. Leioa, ESP

*Corresponding author: Fatima Olaso. Obstetrics and Gynecology Department. Human Reproduction Unit, Cruces University Hospital. Barakaldo, ESP

A B S T R A C T

Introduction: According to World Health Organization, moderate physical activity (PA) is beneficial to health and an effective way to lower the risk of many pathologic conditions. However, no consensus has been reached on the association between PA and success rates of assisted reproduction treatments.

Objective: The purpose of the present study was to determine whether various levels of PA have an influence on ovarian response to controlled stimulation in 'in vitro fertilization' (IVF) or 'intracytoplasmic sperm injection' (ICSI) cycles, defined as number of retrieved and mature oocytes.

Methods: This prospective observational study included 617 infertile women undergoing IVF/ICSI cycles between January 2019 and October 2020. PA was assessed prior to IVF cycle, using the International Physical Activity Questionnaire short form (IPAQ) and triaxial accelerometers. Patients were classified into three groups: low, moderate and high PA.

Results: Globally, the number of retrieved oocytes was similar in all three groups according to IPAQ (9.23 ± 7.72; 8.35 ± 5.57; 8.82 ± 6.38). Something similar happened with the number of mature oocytes (6.97 ± 5.99; 6.84 ± 4.85; 7.05 ± 5.61). PA did not influence the number of oocytes (retrieved or mature) in the majority of clinical subgroups established (age, smoking, body mass index (BMI), anti-mullerian hormone (AMH)). However, in the subgroup of patients having endometriosis the number of mature oocytes was significantly superior in high and moderate vs low PA (p=0.024). In the subgroup of patients with ovulatory disorders there were also more mature oocytes in high and moderate vs low PA (p=0.038).

When performing the analysis according to accelerometer there were globally no significant differences between groups of PA, nor in the majority of clinical subgroups considered. Only in women with normal BMI, high PA was significantly associated with a greater number of collected (p=0.005) and mature oocytes (p=0.004).

Conclusion: Globally, PA had no influence on ovarian response in IVF cycles, defined as number of retrieved and mature oocytes. However, in certain subgroups of patients (endometriosis, ovulatory disorders, normal-BMI) high PA was associated with a superior ovarian response and/or better oocyte maturation.

Keywords: Physical activity; Ovarian response; Oocyte quality; Oocyte maturation; Assisted reproductive technology; In vitro fertilization

Introduction

Successful assisted reproduction treatment requires the interaction of a number of physiological processes. The major determinants are maternal age and good-quality embryos. However, there are other factors, not all of which are well known, that may influence oocyte quality and the likelihood of achieving a successful pregnancy. One of them is physical activity (PA).

Scientific evidence has shown that regular PA is beneficial to health. According to the World Health Organization, moderate PA is an effective way to lower the risk of many pathologic conditions, although its effect on female fertility is not well known[1].

There is solid evidence that both sedentary behavior and excessive PA can be detrimental for female fertility. On one hand, sedentary lifestyle increases the risk of obesity, which is associated with menstrual and ovulatory disorders, higher miscarriage rate and lower pregnancy rate. On the other hand, high-performance-sport involves an increased risk of neuroendocrine and reproductive dysfunction, which may interfere with the achievement of a pregnancy. This disruptive effect of elite-level sport on the menstrual cycle of female athletes has been widely described in scientific literature.

However, no consensus has been reached on the association between PA and success rates of an assisted reproduction treatment. Indeed, assessment of PA is complex. Most published studies used self-administered questionnaires[2-8] and there are few clinical studies with objective evaluation of PA[9-11]. Meta-analyses published to date report a significant increase in clinical pregnancy rates in patients who performed regular PA prior to the IVF cycle[12-14], although it is unknown whether this is due to a better oocyte factor or to a superior endometrial receptivity. Moreover, the type, frequency, volume and intensity for an optimal intervention remain also unclear[14]. Clinical studies evaluating the effect of PA on ovarian response are scarce, although murine models suggest that PA may have a positive impact on it[15-17].

Therefore, the aim of the present study was to determine whether PA influences ovarian response and degree of oocyte maturation in 'in vitro fertilization' (IVF) or 'intracytoplasmic sperm injection' (ICSI) cycles and to analyze the results in certain clinical subgroups: advanced maternal age, smoking, body mass index (BMI), low ovarian reserve and ovarian factor (endometriosis, ovulatory disorders). This article was previously presented as a poster at the European Society of Human Reproduction and Embryology (ESHRE) 39th Annual Meeting on June 26, 2023[18].

Materials and Methods

The study population consisted of 617 infertile women undergoing IVF/ICSI cycles at the Human Reproduction Unit, Cruces University Hospital (Spain), between January 2019 and October 2020.

PA was assessed one month before controlled ovarian stimulation using two methods:

International Standardised PA Questionnaire (IPAQ), which assesses frequency, intensity and duration of PA in the last seven days (n=617 patients)[19] and triaxial accelerometer ActiGraph wGT3X-BT® (Ametris, Pensacola, Florida, USA) (n=105 patients, included in the population of the 617 who answered the IPAQ survey)[20].

All consecutive patients who were going to start an IVF cycle and met inclusion criteria, were asked to complete the survey; most of them accepted, forming the IPAQ group. Of these, n=105 consecutive patients underwent PA assessment by means of an accelerometer between January and October 2020, forming the accelerometer group. Sample size was calculated by means of Granmo Datarus® software (Regicor, IMIM, Barcelona, Spain)[21].

Concerning the design, it was a single-centre prospective observational clinical study. Ethical approval was obtained from the Clinical Research Ethics Committee (CEIC E19/06) and informed consent was signed by all subjects before their participation.

Inclusion criteria were as follows: patients starting fresh IVF/ICSI cycle with own gametes, women aged 18 to 40 years, duration of infertility more than one-year, anti-mullerian hormone (AMH) > 0.4 ng/mL, previous completion of no more than two cycles of ovarian stimulation for IVF/ICSI, BMI <35kg/m², signed informed consent. Exclusion criteria were having started ovarian stimulation or not meeting any of the inclusion criteria. No preimplantation genetic testing for aneuploidy (PGT-A) cycles was included since at the time of the study it was not available at our center.

The following characteristics were collected for each patient: age, weight and height, etiology of infertility, smoking habit and AMH value. BMI was calculated as weight (kg)/height² (m²).

The population's subgroups were defined as follows: advanced maternal age (women aged 37-40 years), smoking (any amount of tobacco), BMI (obese 30-34.9 kg/m², overweight 25-29.9 kg/m², normo-weight 18.5-24.9 kg/m²), low ovarian reserve (AMH <1 ng/mL), ovarian factor (endometriosis or ovulatory disorders).

Assessment of PA: International physical activity questionnaire, short form (IPAQ)

The IPAQ is an international standardized and validated method to assess PA performed during the last seven days by means of a questionnaire. It has shown a good correlation with PA performed in the last weeks and in a typical week[19].

The IPAQ encompasses not only sport or recreational PA but also non-recreational PA (transport, work, housework, etc.). Since people generally follow a routine in their daily lives, reporting PA in the last seven days is usually fairly representative of that person's PA habits.

One month before ovarian stimulation, the patient was invited to fill in the short version of the IPAQ questionnaire, which collects frequency (in days per week), duration (in minutes per week) and intensity of PA performed in the last week.

With regard to intensity of PA, the survey is structured in four groups: vigorous, moderate, walking and sedentary behavior. Intensity of PA was estimated using metabolic equivalents of task (MET). 1 MET (3.5ml O_2/kg/min) represents the energy expenditure at rest. For each PA level, the average MET were calculated using the compendium by Ainsworth attributing 8 MET for vigorous PA, 4 MET for moderate PA and 3.3 MET for walking[22].

Using these measurements, the results of the short version of the IPAQ were calculated, obtaining a total PA score in MET-minutes/week, assessed by the sum of walking, moderate and vigorous MET-minutes.

By means of the IPAQ embedded software, women were classified according to their total PA scores into three levels: low, moderate and high PA. Participants were included at the moderate PA level if they performed a minimum of three days of vigorous PA of at least 20 minutes per day or a minimum of five days of moderate PA and/or walking of at least 30 minutes per day or a minimum of five days of any combination (walking, moderate or intense PA) reaching 600 MET-minutes/week. Women were included at the high PA level if they met one of the following criteria: to perform a minimum of three days of intense PA reaching at least 1500 MET-minutes/week or to perform seven days of any combination (walking, moderate or intense PA) of at least 3000 MET-minutes/week. Participants were included at the low PA level, if they performed no PA or some PA but without meeting criteria for moderate or high categories.

Assessment of PA: Triaxial accelerometer

A subgroup of consecutive patients (n=105), who previously completed the IPAQ survey, were provided with an ActiGraph wGT3X-BT® triaxial accelerometer (Ametris, Pensacola, Florida, USA) to objectively assess PA for seven consecutive days before starting ovarian stimulation (device initialization preset: frequency 100 Hz, Epoch 60s, normal filter option) between January and October 2020[20].

Patients wore the accelerometer on the right hip and data were collected during 16 hours a day. Wearing the device at least four days was considered as a valid week and at least 10 hours of activity was considered as a valid day. Non wear time was established at 90 minutes. It included periods when the subject was asked not to wear the device (sleeping, bathing, swimming) or forgot to wear the device and periods of inactivity, when the device was worn but no PA was performed for more than 90 minutes[23-25].

The acceleration data were recorded in the activity unit 'counts.'

ActiLife ˥® software (Ametris, Pensacola, Florida, USA) was used to process data, using algorithms to convert acceleration data into PA data based on anthropometric characteristics[20]. A positive correlation has been established between the number of counts, oxygen consumption and MET, being possible to calculate PA intensity using validated cut-off points. Those described by Sasaki in 2011 were used: light PA < 2689 counts (1.5 - 3 MET); moderate PA: 2690 - 6166 counts (3 - 6 MET); vigorous PA: 6167 - 9642 counts (6 - 9 MET); very vigorous PA ≥9643 counts (>9 MET) [26].

Accelerometers collected more than 50 PA parameters. Many of them were difficult to interpret clinically, so two representative PA variables were selected for further comparative analysis: total MET (MET-minutes/week) and total 'counts' (counts-min/week).

Treatment protocol

Patients underwent controlled ovarian stimulation with an GnRH antagonist protocol and recombinant and/or urinary gonadotrophin doses between 225-300 IU/day were used.

Follicular growth was monitored by vaginal ultrasound and by determination of serum estradiol and progesterone levels. When three follicles reached 18.5 mm in diameter, final follicular maturation was triggered with hCG 250mcg or GnRH agonist (triptorelin bolus 0.2 ml) if there was a risk of hyperstimulation.

36 hours later, ultrasound-guided oocyte pick-up was scheduled. Assessment of mature oocytes (metaphase II) was based on morphological parameters.

Primary outcome was number of mature oocytes (identified by the presence of the first polar body). Secondary outcome was number of retrieved oocytes.

Statistical analysis

Data were analyzed using IBM® SPSS Statistics 18 (Armonk, New York, USA). Kolmogorov-Smirnov test was performed to verify normality. Since most of the variables studied did not follow a normal distribution, non-parametric tests were used. Results are presented as sample means and standard deviation. Non-parametric continuous quantitative variables were analyzed using Kruskal-Wallis test or U-Mann-Whitney test. Correlation analysis was performed using Rho Spearman test. Statistical significance was defined as $p < 0.05$. In addition, a stratified analysis by clinical subgroups was performed.

Results

Characteristics of the study population

Among the 617 women recruited in the IPAQ study, losses to follow-up were detected for various reasons (spontaneous pregnancies, cancelled cycles, change of medical indication from IVF to intrauterine insemination), so finally n=524 women were included for analysis.

Regarding the accelerometer study, 105 women were provided with the device, of which 88 were eligible, as they wore accelerometer for at least four days. There were three losses to follow-up, so the final number of included women for analysis was n=85.

In the IPAQ population, mean age of women was 34.8 years. Mean BMI was 24.67 kg/m² and mean AMH value was 2.57 ng/mL. In the accelerometer population, mean age of women was 34.9 years and mean BMI was 24.56 kg/m². Mean AMH value was 2.80 ng/mL. **(Table 1)**.

Table 1: Characteristics of 'IPAQ population' and 'Accelerometer population' undergoing IVF.

Characteristics of the population	IPAQ (n=524)			Accelerometer (n=85)		
	Mean	Median	SD	Mean	Median	SD
Age (years)	34.8	36	3.63	34.9	35	3.17
AMH (ng/mL)	2.57	2	2.25	2.8	2.3	2.36
BMI (kg/m²)	24.67	23.47	4.6	24.56	23.28	4.64
Smoking (%)	26.5% (139/524)			23.5% (20/85)		
Number of retrieved oocytes	8.65	7	6.23	8.59	7	6.83
Number of mature oocytes (MII)	6.93	6	5.29	7.31	6	5.8
MET-min/week	2615.82	1836	2542.52	2563.2	2004.1	1612.9
PA level (MET-min/week) (1-3)[a]	2.15	2	0.69	-	-	-
PA level (counts-min/week) (1-4)[b]	-	-	-	1.63	2	0.628
Sedentary time/day (hours)	5.1	4	2.88	-	-	-

[a] 1= low; 2= moderate; 3= high

[b] 1= light; 2= moderate; 3= vigorous; 4= very vigorous

Values are mean, median and SD unless stated otherwise

AMH= anti-mullerian hormone; BMI= body mass index; IPAQ= international physical activity questionnaire; IVF= in vitro fertilization; MET= metabolic equivalent; MII= metaphase II oocyte; PA physical activity; SD= standard deviation

Regarding etiology of infertility among IPAQ population, the most frequent cause was male factor (26.3%), followed by homologous artificial insemination failure (18.9%). Endometriosis accounted for 12.4% of the sample and ovulatory disorders for 5.3%. In the accelerometer sub-study, distribution was similar. The most frequent cause was male factor (28.4%), followed by homologous artificial insemination failure (19.3%). Endometriosis accounted for 15.9% of the sample and ovulatory disorders for 8%.

Regarding to patients' distribution according to PA level -measured in MET- in the IPAQ population, 17.4% (n=91) of women were at the low PA level, 50.5% (n=265) at the moderate level and 32.1% (n=168) at the high level. The cut-off points were 600 and 3000 MET, which corresponded to percentiles p18 and p68 respectively. The groups did not differ in age, BMI, AMH, smoking or infertility etiology. **(Table 2)**.

Table 2: Characteristics of 'IPAQ population' split by clinical subgroups according to PA level

IPAQ population	Low PA (<600 MET) (n=91)	Moderate PA (600-3000 MET) (n=265)	High PA (>3000 MET) (n=168)	p-value
Age (years)	34.86 ± 3.52	34.9 ± 3.67	34.68 ± 3.66	p = 0.73
BMI (kg/m²)	24.52 ± 4.71	24.68 ± 4.63	24.71 ± 4.51	p = 0.911
AMH (ng/mL)	2.36 ± 2.34	2.67 ± 2.30	2.53 ± 2.13	p = 0.482
Smoking (%)	18% (25/139)	47.5% (66/139)	34.5% (48/139)	p = 0.679
Endometriosis	12.9% (8/62)	62.9% (39/62)	24.2% (15/62)	p = 0.161
Ovulatory disorders	18.8% (9/48)	54.2% (26/48)	27.1% (13/48)	p = 0.722

Values are mean ± SD. *Statistical significance was defined as p < 0.05. Statistical analysis: Kruskal-Wallis or Fisher test. AMH= anti-mullerian hormone; BMI= body mass index; IPAQ= international physical activity questionnaire; MET= metabolic equivalent; PA= physical activity

In the accelerometer population, taking the same cut-off points as a reference, 65.9% (n=56) of women were at the moderate PA level and 34.1% (n=29) at the high level. None of the patients (n=0) met the criteria for low PA level. The groups did not differ in age, AMH, smoking or infertility etiology but differed in terms of BMI, being of normo-weight in the moderate PA group and overweight in the high PA group (p=0.001). **(Table 3)**.

Of note, correlation between IPAQ and accelerometer in MET was positive and statistically significant (p=0.031), although weak, with a correlation coefficient Rho Spearman r=0.23.

Table 3: Characteristics of 'Accelerometer population' split by clinical subgroups according to PA level

Accelerometer population	Moderate PA (600-3000 MET) (n=56)	High PA (>3000 MET) (n=29)	p-value
Age (years)	34.46 ± 3.34	35.85 ± 2.58	p = 0.104
BMI (kg/m²)	22.41 ± 3.16	28.74 ± 4.2	p < 0.001*
AMH (ng/mL)	2.65 ± 2.34	3.1 ± 2.44	p = 0.278
Smoking (%)	65% (13/20)	35% (7/20)	p = 1
Endometriosis	78.6% (11/14)	21.4% (3/14)	p = 0.371
Ovulatory disorders	100% (7/7)	0% (0/7)	p = 0.09

Comparative analysis. Association between PA and ovarian response outcomes

Globally, the number of retrieved oocytes was similar in all three groups of PA according to IPAQ (9.23 ± 7.72; 8.35 ± 5.57; 8.82 ± 6.38). Something similar happened with the number of mature oocytes (6.97 ± 5.99; 6.84 ± 4.85; 7.05 ± 5.61). **(Table 4)**.

Table 4: Association between PA level in global 'IPAQ population' (n=524) and controlled ovarian stimulation outcome.

	Low PA (n=91)	Moderate PA (n=265)	High PA (n=168)	p-value
Retrieved oocytes	9.23 ± 7.72	8.35 ± 5.57	8.82 ± 6.38	$p = 0.85$
Mature oocytes	6.97 ± 5.99	6.84 ± 4.85	7.05 ± 5.61	$p = 0.81$

Values are mean $\pm$ SD. *Statistical significance was defined as $p < 0.05$. Statistical analysis: Kruskal-Wallis test. IPAQ= international physical activity questionnaire; PA= physical activity.

When data were split regarding a number of clinical parameters (age, smoking, BMI, AMH), PA did not affect differently neither to retrieved nor mature oocytes.

However, when stratifying by etiology of infertility, there were statistically significant differences in the number of mature oocytes. In the subgroup of patients having endometriosis the number of mature oocytes was significantly superior at high (8.40 ± 4.79) and moderate (7.71 ± 4.56) vs low PA level (3.63 ± 4.0) (p=0.024). In the subgroup of ovulatory disorders there were also more mature oocytes at high (11.89 ± 5.42) and moderate level (8.0 ± 4.44) vs low PA level (3.5 ± 3.54) (p=0.038). **(Table 5)**.

In the analysis according to accelerometer there was globally no association between PA level (expressed in MET and counts) and ovarian response. When data were split regarding a number of clinical parameters (age, smoking, BMI, AMH), PA did not affect differently to oocyte number, neither retrieved nor mature. **(Table 6)**.

However, when stratifying by BMI, statistical significance was found. In normo-weight women, high PA level (expressed in MET) was significantly associated with a greater number of collected oocytes (20.83 ± 13.63) and mature oocytes (17.5 ± 10.78) compared to moderate PA level (7.56 ± 5.65; 6.4 ± 4.87 respectively) (p=0.005; p=0.004 respectively). When stratifying by infertility etiology, no significant differences were found in the subgroup of patients having endometriosis. More retrieved oocytes (9.33 ± 5.69) and more mature oocytes (7.33 ± 5.86) were obtained at high PA level compared to moderate level (6.73 ± 3.88; 6.0 ± 3.82 respectively), but without statistical significance (p=0.435; p=0.814 respectively). In patients with ovulatory disorders, it was not possible to perform the analysis due to small sample size (n=7) and moreover because all women were at the same PA level. **(Table 7)**.

Table 5: Association between PA level in 'IPAQ population' (n=524) and number of retrieved and mature oocytes among clinical subgroups.

IPAQ population	Retrieved oocytes				Mature oocytes			
	Low PA	Moderate PA	High PA	p-value	Low PA	Moderate PA	High PA	p-value
Age (37-40 years) (n=215)	6.94 ± 5.31	7.48 ± 5.20	9.39 ± 7.18	$p = 0.115$	5.85 ± 4.70	6.16 ± 4.49	7.58 ± 6.30	$p = 0.246$
BMI: normal (18.5-24,9 kg/m²) (n=304)	9.31 ± 8.39	8.51 ± 5.77	8.78 ± 6.90	$p = 0.990$	6.92 ± 6.26	7.06 ± 5.14	7.05 ± 6.18	$p = 0.630$
BMI: overweight ($\geq$ 25 kg/m²) (n=244)	8.75 ± 7.14	8.15 ± 5.46	8.57 ± 5.38	$p = 0.830$	6.47 ± 5.71	6.53 ± 4.54	6.94 ± 4.81	$p = 0.679$
BMI: obesity ($\geq$ 30 kg/m²) (n=90)	6.80 ± 5.16	7.88 ± 5.11	9.30 ± 5.06	$p = 0.25$	5.40 ± 3.31	6.06 ± 4.32	7.59 ± 5.54	$p = 0.399$
AMH < 1 ng/mL (n=115)	4.67 ± 3.45	4.41 ± 2.98	4.73 ± 3.26	$p = 0.837$	4.0 ± 3.34	3.67 ± 2.69	3.97 ± 3.19	$p = 0.979$
Smoking (n=139)	6.47 ± 4.44	8.0 ± 4.88	8.12 ± 5.74	$p = 0.461$	4.63 ± 3.18	6.46 ± 4.15	6.70 ± 5.65	$p = 0.322$
Endometriosis (n=61)	5.63 ± 4.69	9.24 ± 5.43	10.33 ± 5.11	$p = 0.144$	3.63 ± 4.0*	7.71 ± 4.56	8.40 ± 4.79*	**$p = 0.024$***
Ovulatory disorders (n=26)	4.0 ± 4.24	9.8 ± 5.61	15.11 ± 6.49	$p = 0.057$	3.50 ± 3.54*	8.0 ± 4.44	11.89 ± 5.42*	**$p = 0.038$***

Values are mean $\pm$ SD. *Statistical significance was defined as $p < 0.05$. Statistical analysis: Kruskal- Wallis. AMH= anti-mullerian hormone; BMI= body mass index; IPAQ= international physical activity questionnaire; PA= physical activity

Table 6: Association between PA level in global 'Accelerometer population' (n=85) and controlled ovarian stimulation outcome

	MET-min/week			Counts-min/week				
	Moderate PA (n=56)	High PA (n=29)	p-value	Light PA (n=37)	Moderate PA (n=43)	Vigorous PA (n=4)	Very vigorous PA	p-value
	(600 – 3000)	(> 3000)		(<2690)	(2690 – 6166)	(6167 – 9642)	(> 9643)	
Retrieved oocytes	7.93 ± 5.38	9.93 ± 9.10	$p = 0.506$	8.49 ± 5.77	8.84 ± 7.72	6.75 ± 8.18	9.0 (n=1)	$p = 0.721$
Mature oocytes	6.79 ± 4.63	8.36 ± 7.64	$p = 0.687$	7.22 ± 4.99	7.42 ± 6.41	6.75 ± 8.18	8.0 (n=1)	$p = 0.774$

Values are mean $\pm$ SD. *Statistical significance was defined as $p < 0.05$. Statistical analysis: U Mann-Whitney or Kruskal-Wallis. MET= metabolic equivalent; PA= physical activity

Table 7: Association between PA level (MET-min/week) in 'Accelerometer population' (n=85) and number of retrieved and mature oocytes among clinical subgroups.

Accelerometer population	Retrieved oocytes			Mature oocytes		
	Moderate PA	High PA	p-value	Moderate PA	High PA	p-value
	(600 – 3000 MET)	(> 3000 MET)		(600 – 3000 MET)	(> 3000 MET)	
Age (37-40 years) (n=33)	6.71 ± 4.57	11.50 ± 10.41	$p = 0.129$	5.71 ± 3.89	9.69 ± 8.72	$p = 0.181$
BMI: normal (18.5-24,9 kg/m²) (n=49)	7.56 ± 5.65	20.83 ± 13.63	**$p = 0.005$***	6.40 ± 4.87	17.50 ± 10.78	**$p = 0.004$***
BMI: overweight ($\geq$ 25 kg/m²) (n=36)	8.50 ± 4.52	6.95 ± 4.33	$p = 0.219$	7.33 ± 3.60	5.86 ± 4.12	$p = 0.107$
BMI: obesity ($\geq$ 30 kg/m²) (n=13)	18.0 (n=1)	7.09 ± 5.67	$p = 0.188$	12.0 (n=1)	6.18 ± 5.46	$p = 0.308$
AMH < 1 ng/mL (n=14)	3.20 ± 2.04	7.25 ± 3.86	$p = 0.085$	2.80 ± 2.15	6.50 ± 3.11	$p = 0.062$
Smoking (n=20)	7.0 ± 4.86	5.67 ± 2.81	$p = 0.741$	6.0 ± 4.45	4.0 ± 2.37	$p = 0.397$
Endometriosis (n=14)	6.73 ± 3.88	9.33 ± 5.69	$p = 0.435$	6.0 ± 3.82	7.33 ± 5.86	$p = 0.814$
Ovulatory disorders (n=7)	7.29 ± 5.41	-	-	6.43 ± 4.79	-	-

Values are mean $\pm$ SD. *Statistical significance was defined as $p < 0.05$. Statistical analysis: U Mann-Whitney. AMH= anti-mullerian hormone; BMI= body mass index; MET= metabolic equivalent; PA= physical activity

Discussion

There is broad consensus on the positive impact of regular, aerobic, moderate-intensity PA on health. Benefits include improved insulin-sensitivity, body weight control and the development of cardiovascular, respiratory, metabolic and immunological adaptations[1,27]. However, it is unclear whether PA could produce any local beneficial in the ovary that could increase the number of total or mature oocytes and therefore improve the outcome of an IVF cycle.

In the present study, global PA assessed by IPAQ or by accelerometer did not influence ovarian response to stimulation in the IVF cycle. However, in certain clinical subgroups (endometriosis, ovulatory disorders or normal BMI) high PA was significantly associated with a superior ovarian response and/or better oocyte maturation. High PA occurred mainly in those patients who practiced regular, planned and structured PA, i.e. 'physical exercise', which generates anatomical and functional adaptations after several weeks if a certain threshold of PA is reached. This threshold has not yet been established in relation to IVF.

Our study has been primarily aimed at assessing the influence of PA on ovarian response, whereas some of the previous research focused mainly on pregnancy rate[9-13]. This may explain some of the discrepancies, as a higher pregnancy rate may be due to a better oocyte factor or superior endometrial receptivity. In this study we chose to focus on the oocyte factor as it is easily measurable, objectively. Analysing pregnancy rates involves, on the one hand, consideration of the endometrial factor, whose independent assessment is conceptually and methodologically complicated. Unquestionably the best way to measure both ovarian and endometrial response is through pregnancy rates. However, this brings with it the difficulty of including the male factor, which should not be associated with women's PA.

In previous studies that referred to pregnancy rate in IVF in relation to PA, some authors found no association or reported a negative effect of PA[6,8,28,29], although most authors found a statistically significant higher pregnancy rate in regular PA groups[2,5,7,10,13]. Of the three authors who also analysed the oocyte factor[3,10,11], Söritsa and Prémusz found a higher number of retrieved oocytes in relation to PA, in contrast to Ferreira, who found no difference. Only Prémusz analysed oocyte quality, reporting more mature oocytes in the moderate PA group. Speculation could be made as to whether PA has a positive impact on the endometrium or on the oocyte. Regarding the endometrium, it could increase vascular flow or act as an immunomodulator, favouring embryo implantation; although two studies in which PA was measured by accelerometer from embryo transfer to pregnancy test found no significant differences in pregnancy rate between active and sedentary women[2,11]. Two meta-analyses have explored the impact of PA on IVF cycle outcomes[12,13]. Rao concluded that PA for more than 2.5 hours per week prior to IVF/ICSI cycle significantly improved clinical pregnancy and livebirth rates[12]. Subsequently, Kakargia reported that PA prior to the IVF/ICSI cycle improved clinical pregnancy rate, although the authors found no significant differences in implantation, miscarriage or livebirth rates[13].

In the present study, a superior ovarian response and/ or higher number of mature oocytes was observed in certain clinical subgroups (endometriosis, ovulatory disorders and normal BMI). This suggests that certain patient profiles may be candidates for PA as part of a customized therapeutic strategy. It seems reasonable to suppose that, just as different clinical parameters have a different impact on IVF outcomes, perhaps PA could have a differential impact according to coexisting clinical variables (maternal age, ovarian reserve, smoking, obesity, infertility etiology, etc.). Of these clinical parameters, the one that has received the most attention is obesity/overweight, due to its clear inverse association with PA.

Scientific evidence shows a worse response to stimulation, poorer oocyte quality and lower clinical pregnancy rate in obese women. It has been suggested that obesity induces chronic low-grade systemic inflammation. In the present study there was no association between ovarian response and PA level, as reported by Moran or Kiel[28,30]. Palomba, on the contrary, reported better IVF cycle outcome in obese women who performed regular PA[7].

In women with polycystic ovarian syndrome, moderate PA is recommended in the treatment of this pathology and has been associated with increased spontaneous pregnancy and live birth rates[14]. In the present study, by IPAQ, significantly more mature oocytes were collected at the high PA level.

As for endometriosis, it has been reported that a suboptimal microenvironment in the follicle, where a proinflammatory phenotype predominates as well as oxidative stress, would negatively affect oocyte cytoplasmatic competence[17]. In the present IPAQ study, significantly higher numbers of mature oocytes were obtained at the high and moderate PA level versus low PA level.

Among the strengths of this study, it should be noted that it was the second in terms of sample size after Morris[6], using questionnaires as a method for assessing PA. Concerning the validated specific IPAQ questionnaire, this study was the one with the largest sample size. Furthermore, it was the one with the largest sample size performing a double analysis, IPAQ and triaxial accelerometer. The objective assessment of PA can be considered a strength of the study, as well as its prospective design.

Secondly, an analysis by clinical subgroups was performed allowing to analyse the influence of PA in different clinical conditions. It must be highlighted that, as a consequence of the many clinical subgroups considered, our study could have obtained by chance in some cases p values < 0.05. It is well known that, when performing multiple hypothesis tests, the probability of making one or more false discoveries or type I errors, increases.

There are some limitations to this study, so results should be interpreted with caution. Firstly, although using a validated questionnaire -as IPAQ- to assess PA, this method has some disadvantages such as subjectivity, recall bias or overestimation of performed PA. On the other hand, accelerometers show the inconvenience of having to be removed during aquatic activities or presenting a surveillance bias. Secondly, this was an observational study. Despite taking into account some confounding factors, it is possible that high PA may be associated with certain parameters that, in themselves, could be related to a better outcome of IVF cycle, such as healthy lifestyle habits, diet, higher socioeconomic status and lower adiposity, among others. Thirdly, sample size after stratification was small, especially in the accelerometer study.

Conclusion

PA has multisystemic benefits for human health. Nevertheless, evidence so far is insufficient to draw robust conclusions about the impact of PA on ovarian response.

In the present study, differences in short-term PA among women undergoing IVF/ICSI cycles had globally no influence on ovarian response, defined as number of retrieved and mature oocytes. However, in certain clinical subgroups (endometriosis, ovulatory disorders, normal-BMI) high PA was associated with a superior ovarian response and better oocyte maturation. These findings open up new lines of research in relation to PA, taking into account patients' underlying conditions and etiology of infertility. More prospective clinical studies are needed specifically in these subgroups to determine whether there is an optimal pattern of PA in relation to type, frequency, volume and intensity in order to establish personalized recommendations.

Abbreviations

AMH= anti-mullerian hormone; ART= assisted reproduction technology; BMI= body mass index; β-hCG= human chorionic gonadotrophin; COS= controlled ovarian stimulation; ICSI= intracytoplasmic sperm injection; IPAQ= international physical activity questionnaire; IU= international units; IVF= in vitro fertilization; Kcal= Kilocalories; MET= metabolic equivalent; MII= metaphase II oocyte; PA= physical activity; PGT= preimplantation genetic testing; SD= standard deviation

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Clinical Research Ethics Committee (CEIC E19/06) and informed consent was signed by all subjects before their participation.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

Not applicable. The authors report no financial or commercial conflicts of interest

Funding

Not applicable

Authors' Contributions

FO and RM conceived and designed research. FO conducted experiments. RM, IE and JI contributed analytical tools. FO and IE analyzed data. FO wrote the manuscript. All authors read and approved the manuscript.

References

1. Bull FC, Al-Ansari SS, Biddle S, et al.: World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020;54:1451-1462.

2. Evenson KR, Calhoun KC, Herring AH, et al. Association of physical activity in the past year and immediately after in vitro fertilization on pregnancy. Fertil Steril 2014;101:1047-1054.

3. Ferreira RC, Halpern G, Figueira Rde C, et al. Physical activity, obesity and eating habits can influence assisted reproduction outcomes. Womens Health (Lond) 2010, 6:517-524.

4. Gaskins AJ, Williams PL, Keller MG, et al. EARTH Study Team: Maternal physical and sedentary activities in relation to reproductive outcomes following IVF. Reprod Biomed Online 2016;33:513-521.

5. Kucuk M, Doymaz F, Urman B. Effect of energy expenditure and physical activity on the outcomes of assisted reproduction treatment. Reprod Biomed Online 2010;20:274-279.

6. Morris SN, Missmer SA, Cramer DW, et al. Effects of lifetime exercise on the outcome of in vitro fertilization. Obstet Gynecol 2006;108:938-945.

7. Palomba S, Falbo A, Valli B, et al. Physical activity before IVF and ICSI cycles in infertile obese women: an observational cohort study. Reprod Biomed Online 2014;29:72-79.

8. Ramezanzadeh F, Kazemi A, Yavari P, et al. Impact of body mass index versus physical activity and calorie intake on assisted reproduction outcomes. Eur J Obstet Gynecol Reprod Biol 2012;163:52-56.

9. Läänelaid S ortega FB, Kunovac Kallak T, et al. Physical and sedentary activities in association with reproductive outcomes among couples seeking infertility treatment: a prospective cohort study. Int J Environ Res Public Health 2021;18:2718.

10. Prémusz V, Makai A, Perjés B, et al. Multicausal analysis on psychosocial and lifestyle factors among patients undergoing assisted reproductive therapy - with special regard to self-reported and objective measures of pre-treatment habitual physical activity. BMC Public Health 2021;21:1480.

11. Sõritsa D, Mäestu E, Nuut M, et al. Maternal physical activity and sedentary behavior before and during in vitro fertilization treatment: a longitudinal study exploring the associations with controlled ovarian stimulation and pregnancy outcomes. J Assist Reprod Genet 2020;37:1869-1881.

12. Rao M, Zeng Z, Tang L. Maternal physical activity before IVF/ICSI cycles improves clinical pregnancy rate and live birth rate: a systematic review and meta-analysis. Reprod Biol Endocrinol 2018;16:11.

13. Kakargia E, Mamalakis E, Frountzas M, et al. The role of maternal physical activity on in vitro fertilization outcomes: a systematic review and meta-analysis. Arch Gynecol Obstet 2023;307:1667-1676.

14. Mena GP, Mielke GI, Brown WJ. The effect of physical activity on reproductive health outcomes in young women: a systematic review and meta-analysis. Hum Reprod Update 2019;25:541-563.

15. Boudoures AL, Chi M, Thompson A, et al. The effects of voluntary exercise on oocyte quality in a diet-induced obese murine model. Reproduction 2016;151:261-270.

16. Faraci C, Annis S, Jin J, et al. Impact of exercise on oocyte quality in the POLG mitochondrial DNA mutator mouse. Reproduction 2018;156:185-194.

17. Montenegro ML, Bonocher CM, Meola J, et al. Effect of physical exercise on endometriosis experimentally induced in rats. Reprod Sci 2019;26:785-793.

18. Olaso F, Mendoza R, Echeverria I, et al. Impact of physical activity (PA) on oocyte quality: a prospective study among IVF/ICSI patients. Hum Reprod 2023;38.

19. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381-1395.

20. ActiGraph (Ametris) 2020.

21. Granmo Datarus 2019.

22. Ainsworth BE, Haskell WL, Herrmann SD, et al. Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575-1581.

23. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc 1998;30:777-781.

24. Matthews CE. Physical activity in the United States measured by accelerometer: comment. Med Sci Sports Exerc 2008;40:1188.

25. Migueles JH, Cadenas-Sanchez C, Ekelund U, et al. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. Sports Med 2017;47:1821-1845.

26. Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph activity monitors. J Sci Med Sport 2011;14:411-416.

27. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports 2015;25:1-72.

28. Moran L, Tsagareli V, Norman R, Noake M. Diet and IVF pilot study: short-term weight loss improves pregnancy rates in overweight/obese women undertaking IVF. Aust N Z J Obstet Gynaecol 2011;51:455-459.

29. Ricci E, Noli S, Ferrari S, et al. Pretreatment maternal lifestyle and outcomes of assisted reproduction: an Italian cohort study. BMJ Open 2020;10:038837.

30. Kiel IA, Lundgren KM, Mørkved S, et al. Women undergoing assisted fertilization and high-intensity interval training: a pilot randomized controlled trial. BMJ Open Sport Exerc Med 2018;4:e000387.