Lay summary
Infertility affects ~1 in 7 couples with many and varied causes, including lifestyle factors such as smoking, alcohol and diet. Lifestyle changes are low cost unimposing options to implement in routine fertility care. Information on regular physical activity is not currently enquired from women and no agreement regarding best levels of exercise exists for fertility patients. We aimed to determine exercise habits of women attending the one stop infertility (OSI) clinic. 250 women attending OSI clinic over a period of 9 months, completed a questionnaire collecting data on their exercise habits. The levels of physical activity performed varied widely from vigorous exercise on ≥5 days/week, to no moderate or high intensity activities across the whole week. The majority of women did no structured exercise (72%). These novel data highlight the variations in form type and intensity of exercise women who attend OSI clinics perform. Currently there is no existing evidence and/or guidelines to explicitly inform women attempting to conceive regarding the recommended physical activity levels. Physical activity is a modifiable, affordable, and feasible lifestyle choice that is not currently acknowledged in the fertility setting and has the potential to improve fertility.
Habitual physical activity levels in women attending the one stop infertility clinic: A prospective cross-sectional observational study

Running title – Physical activity in women seeking fertility treatment

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Abstract

Optimisation of lifestyle factors such as smoking and alcohol are encouraged to improve fecundability rates in the fertility setting. Currently, routine fertility consultations do not involve counselling or imparting advice regarding habitual physical activity (PA) and/or structured exercise, despite data showing that vigorous PA can be associated with delayed time to pregnancy. Therefore, this study aimed to determine habitual PA in a sample of women attending the one stop infertility (OSI) clinic. 250 women attending a large tertiary level NHS fertility unit prospectively anonymously completed a questionnaire over a period of 9 months. Participant’s (mean age 34±5 years, mean BMI 29±7 kg/m²) habitual PA levels varied from vigorous exercise on ≥5 days/week (8%, n=17), to no moderate or high intensity activities across the whole week (66%, n=29). The majority of women reported no structured exercise (72%, n=179). No association was identified between any domain of PA and BMI, age, alcohol units, regular periods, or time spent trying to conceive (P > 0.05). Participant’s habitual PA levels varied widely and no association between any domain of PA and background of the women was identified. No existing evidence and/or guidelines to explicitly inform women attempting to conceive regarding recommended PA levels are available, despite PA being a modifiable, affordable, and feasible lifestyle choice with the possible potential to improve fertility. A large-scale, clinical trial assessing effects of PA on fecundability is warranted to gain insights into the potential of this lifestyle factor to improve fertility outcomes and to explore the underlying biological mechanisms involved.

Keywords – Physical activity, exercise, fertility, infertility, conception

Lay summary

Infertility affects ~1 in 7 couples with many and varied causes, including lifestyle factors such as smoking, alcohol and diet. Lifestyle changes are low cost unimposing options to implement in routine fertility care. Information on regular physical activity is not currently enquired from
women and no agreement regarding best levels of exercise exists for fertility patients. We
aimed to determine exercise habits of women attending the one stop infertility (OSI) clinic. 250
women attending OSI clinic over a period of 9 months, completed a questionnaire collecting
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vigorous exercise on ≥5 days/week, to no moderate or high intensity activities across the
whole week. The majority of women did no structured exercise (72%). These novel data
highlight the variations in form type and intensity of exercise women who attend OSI clinics
perform. Currently there is no existing evidence and/or guidelines to explicitly inform women
attempting to conceive regarding the recommended physical activity levels. Physical activity
is a modifiable, affordable, and feasible lifestyle choice that is not currently acknowledged in
the fertility setting and has the potential to improve fertility.

Introduction

Infertility is defined as a reproductive disease, described as the failure to achieve a clinical
pregnancy within 12 months or more, of regular unprotected sexual intercourse (Zegers-
Hochschild et al. 2009). Approximately 1 in 7 couples are likely to experience difficulty
conceiving (NICE 2017; NHS). The main causes often overlap and, in the UK, approximately
40% of cases identify disorders in both the man and woman (NICE 2017). They include:
unexplained infertility (25%), ovulatory disorders (25%), tubal damage (20%), factors in the
male causing infertility (30%), and uterine or peritoneal disorders (10%) (NICE 2017). Infertility
causes a huge burden on those couples affected with both psychological and physical strain
(Schmidt 2006). Some lifestyle and recreational factors, such as alcohol/drug consumption,
smoking, and hobbies, can affect fecundability rates and couples are counselled regarding
optimisation of these, accordingly (NICE 2017; Britton 2016; Ricci et al. 2017; Imterat et al.
2019; Ser mondade et al. 2019; Ayton 2019).

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Currently, routine fertility consultations do not involve counselling or imparting advice regarding habitual physical activity (PA) and/or structured exercise despite data from two large observational fecundability studies showing that vigorous PA was associated with delayed time to pregnancy in women with a normal BMI not currently seeking fertility care (McKinnon et al. 2016; Wise et al. 2012). Numerous other studies have examined the association between exercise and specific fertility outcomes but the available evidence remains equivocal (Ahrens et al. 2014; Bullen et al. 1985; Mena, Mielke, and Brown 2020). This variability within the literature holds true for women living with polycystic ovarian syndrome (PCOS), a heterogenous condition frequently associated with ovulatory disorders. It has been observed that increased PA and exercise in these women improves overall health outcomes and symptom presentation, but findings related to fertility outcomes are contradictory and relate more to weight status than PA levels (Dos Santos et al. 2020; Kite et al. 2019; Harrison et al. 2011; Stepto et al. 2019; Sprung et al. 2013). With this in mind, a change in habitual PA is potentially a cost effective, minimally invasive adjunct, associated with general health benefits, for women to consider as part of their routine fertility care.

Therefore, the aim of the current study was to determine habitual PA in a sample of women attending the one stop infertility (OSI) clinic. Furthermore, we sought to assess the willingness of these women to participate in further research examining the influence of PA on fertility outcomes.

**Materials and methods**

The questionnaire was distributed to 350 non-pregnant females, aged 34±5 years, who attended the OSI clinic at The Hewitt Fertility Centre, Liverpool (a specialist tertiary referral fertility centre), between November 2020 and July 2021. Eligibility was based on three simple criteria; i) non-pregnant women; ii) aged 18-42 years; iii) attending the clinic for fertility consultation.
Ethical approval

This observational study conformed to the Declaration of Helsinki and was approved by the London-Bloomsbury Research Ethics Committee (REC: 20/PR/0458). All participants were informed of the protocol verbally and in writing prior to completion of the questionnaire. This detailed that consent is assumed on the voluntary return of the completed questionnaire (which did not contain any personal identifiable data).

Demographics

Women who completed the International Physical Activity Questionnaire short form (IPAQ-SF) self-reported their age, height, weight, ethnicity, smoking status, alcohol consumption, occurrence of regular periods, gravidity, parity, length of time trying to conceive, diagnosis of fertility pathology, previous fertility treatment, medical conditions, and regular medication.

International Physical Activity Questionnaire

The IPAQ-SF, which has been validated and successfully administered to similar groups (eg. female clinical groups (Russo et al. 2018)), was identified as the most suitable, validated, clinical tool for assessing contemporaneous self-reported habitual PA and exercise at a population observation level (Craig et al. 2003). The IPAQ-SF requires participants to report how many days they walked and did moderate, or vigorous PA for at least 10 minutes at a time in the 7 days prior to completing the questionnaire. PA measured via the IPAQ-SF is classified as high, moderate, and low. High-level PA was defined as vigorous activity, of at least 20 minutes per day, occurring on ≥3 days per week, achieving a minimum of 1500 metabolic equivalent (MET) minutes per week in total; or 7 days of any combination of walking, moderate-intensity or vigorous intensity activities, achieving a minimum of 3000 MET minutes per week in total. Moderate PA was defined as any of the following: vigorous activity, of at least 20 minutes per day, occurring on ≥3 days per week; ≥5 days of moderate intensity activity and/or walking of at least 30 minutes per day; ≥5 days of any combination of walking, moderate-intensity or vigorous intensity activities; all achieving a minimum of at least 600
Metabolic Equivalent (MET) minutes per week in total. Participants were classified as low PA if they did not achieve moderate or high levels of PA (Cheng 2016.).

Further research

Women were also asked if they would be interested in participating in a further research study examining the effects of PA on fertility outcomes.

Statistical Analysis

Initially, summary data were extracted and reported; mean and standard deviation for continuous data, and percentages for categorical data. Correlations between PA and lifestyle factors were assessed using Pearson’s correlation coefficient. The alpha level of statistical significance was set at $P<0.05$. Statistical analysis was performed using SPSS for Windows (Version 26.0, SPSS).

Results

A response rate of 71.4% (250/350) was observed in this study, not all participating women completed all sections of the demographic data collection and IPAQ-SF.

Descriptive Characteristics

250 data sets were analysed from respondents (age 34 ± 5 years, BMI 29 ± 7 kg/m²) (Table I). Sixty percent ($n=143$) of the women had never had a pregnancy, and 82% ($n=199$) did not have children. Most women (64.4%, $n=161$) had no diagnosed cause for infertility (first tertiary clinic appointment and therefore most had not had investigations). The common causes documented included: PCOS (15.2%, $n=38$), male factor (9.2%, $n=23$), endometriosis (3.6%, $n=9$), and premature ovarian failure (POF) (2.8%, $n=7$). 72% ($n=180$) had no past medical history of note. Commonly reported medical co-morbidities included asthma (9.2%, $n=23$), depression (5.2%, $n=13$), migraines (3.2%, $n=8$), hypothyroid (2.8%, $n=7$), and hypertension (2%, $n=5$). The majority (70.4%, $n=176$) of women were not taking regular, prescribed
medications. Amongst those who reported regular medication use, antidepressants (8%, n=20) or inhalers (6.4%, n=16) were most commonly listed.

**Habitual PA observations**

Out of the 229 women who fully and accurately completed the IPAQ-SF, approximately half of the participants achieved the aforementioned criteria for moderate levels of PA, whilst approximately a quarter of participants achieved low or high levels (Table II). Women who reported taking part in structured exercise (n=71, 28%) spent 172±105 min/week doing this.

On average, walking was performed on 5 ± 2 days/week for 61±88 min/day. Amongst women who reported walking ≥10 min daily (46%, n=98), walking was performed 79±103 min/day.

Only 7% (n=15) of women reported walking for 0 min/week, whilst time spent sitting was 5 ± 4 hours/day.

**Correlations**

Analysis of all physical activity variables, measured using the IPAQ-SF, revealed no significant correlation with demographic variables including age, BMI, units of alcohol consumed, regular periods, or time trying to conceive (P>0.05).

**Acceptability**

Of the 234 women who responded to the question querying whether they would be interested in participating in future research investigating the effect of PA on fertility, 31.2% (n=73) answered yes. Amongst those who answered yes, women recorded the maximum amount of time they would be happy to delay fertility treatment if they took part in a future research trial (Table III).

**Discussion**
Habitual PA in women experiencing infertility is unknown. Furthermore, PA is not currently considered during routine fertility care consultations, nor are there any clinical guidelines available to advise women aiming to conceive regarding safe frequency, duration, intensity and modes of PA. The aim of the current study was therefore, to determine habitual PA in a sample of women attending the OSI clinic. Our study found a wide variation of PA levels and types with some women reporting performing vigorous exercise on ≥5 days per week (8%, n=17), a large proportion of women (29%, n=66) stating that they do no moderate or high intensity activities across the whole week, while most women reporting no structured exercise (72%, n=179).

Evidence is available from large prospective observational studies informing that vigorous PA could be detrimental to fecundability in a population of women, with a normal BMI, not seeking fertility treatment (Wise et al. 2012; McKinnon et al. 2016) and change in menstrual cycles is also seen in women participating in vigorous exercise (Ellison PT 1985; De Souza et al. 1998; Bullen et al. 1985). Despite this, there is lack of robust evidence and guidelines relating to women seeking fertility treatment to advise on how best to incorporate PA into their daily routine. Importantly, a considerable proportion of women in our cohort were outside the healthy BMI range (63%, n=138), which has consistently been demonstrated within the literature to decrease fecundability, as well as increase the risk of miscarriage and pregnancy complications (Silvestris et al. 2018; Satpathy et al. 2008; Cozzolino et al. 2021). Therefore, in the context of increasing rates of women seeking fertility support, it is important to understand whether habitual PA could act as a non-pharmacological aid, with or without weight loss and ensure that we are providing our patients with best evidence-based care.

A recent systematic review has shown that PA may improve pregnancy rates in women with reproductive health problems, but the mode, intensity, frequency, and duration of optimal PA intervention, and the role of PA independent of weight loss, remains unclear (Mena, Mielke, and Brown 2019). In a cohort of obese women undergoing IVF, those who performed regular
PA prior to assisted reproduction experienced higher success rates, (39% vs. 16% in sedentary women, \( P=0.002 \)) and improved live birth rates (24.4% vs. 7.4%, \( P=0.004 \)) compared with women who did not, irrespective of weight loss (Palomba et al. 2014). This evidence provides encouraging support for the use of PA recommendations/guidelines for obese women, who are aiming to conceive. Furthermore, a 2002 questionnaire-based prospective cohort study, originally designed to examine the association between lifestyle (smoking/exercise) and diet with breast cancer and other major diseases, found that each hour of vigorous activity undertaken per week was associated with a 7% lower relative risk of ovulatory infertility (5% on adjustment of BMI) (Rich-Edwards et al. 2002). This is in contrast to other studies examining ovulatory infertility and exercise (Ellison PT 1985; De Souza et al. 1998; Bullen et al. 1985), and should perhaps be interpreted with caution as the outcomes do not relate to the original question asked within the study.

PCOS is recognised as the leading cause of anovulatory infertility and affects 12%-18% of women of reproductive age (March et al. 2010), with obesity prevalent in 40-88% of affected women (Balen et al. 1995; Azziz et al. 2004; Lim et al. 2012). Lifestyle modification, including PA, has been seen as a first line approach in PCOS management (Teede et al. 2011). In a systematic review, women with PCOS were shown to have higher pregnancy rates [RR 1.59, 95% CI (1.06, 2.38); five studies] and live birth rates [RR 2.45, 95% CI (1.24, 4.83); two observations] in PA intervention groups, compared with non-intervention controls. Further analysis showed no significant differences in improving menstrual regularity, ovulation, and conception rates between the PA intervention and comparison groups (Mena, Mielke, and Brown 2019). Despite the high prevalence of PCOS, and the indisputable link with fertility, no robust evidence is currently available to recommend the optimum mode and volume of PA (Harrison et al. 2011; Dos Santos et al. 2020; Lim et al. 2019).

Over a quarter of the women in our cohort did low levels of PA and a quarter did high levels of PA, both could interestingly be impacting their fertility. A study looking at sedentary
behaviour and idiopathic infertility showed that sedentary behaviour (OR 3.61; 95%CI, 1.58, 8.24) was shown to be associated with infertility, but PA was not associated with fertility (Foucaut et al. 2019). Conversely, evidence is also available demonstrating that high intensity exercise is detrimental for fertility, causing a decreased length of luteal phase, anovulatory cycles, and eventually, amenorrhoea (Hakimi and Cameron 2017; Sophie Gibson et al. 2020; Huhmann 2020; Ellison PT 1985; Green et al. 1986; De Souza et al. 1998; Bullen et al. 1985).

A large population-based health survey reported that increased frequency, duration, and intensity of PA were associated with increased subfertility. Women who were active on most days of the week were 3.2 times more likely to have fertility problems than inactive women, with exercising to exhaustion associated with 2.3 times the odds of fertility problems, vs. low intensity exercise (Gudmundsdottir, Flanders, and Augestad 2009). High intensity exercise has also been associated with a 5-fold increase in IVF cycle cancellation, a 2.5-fold increase in failed implantation, a 30% lower chance of successful pregnancy, and a 50% reduction in live births compared with women who reported no regular PA in a large prospective study (Morris et al. 2006). A recent systematic review investigating the effect of exercise on ovulation, showed an increased risk of anovulation in extremely heavy exercisers (>60min/day), but vigorous exercise (30-60 min/day) was associated with reduced risk of anovulatory infertility (Hakimi and Cameron 2017).

Our study is novel, since we elicit the habitual PA of the women who attend the OSI clinic and do not provide a prescribed intervention assuming that one intervention would suit all women. We included all women regardless of their BMI or any previously diagnosed pathology ensuring a representative sample of women who struggle with fertility and attend the OSI clinic. Unfortunately, questionnaires have been reported to overestimate PA in women and, as such, objective measurements have been recommended (Bell et al. 2013). However, they remain valuable to define types and profiles of activity (Craig et al. 2003), and would provide the preliminary information pertinent to this cohort of patients, thus were selected as the best methodological approach.
PA is an easily modifiable, affordable, and feasible lifestyle choice, which is currently ignored in the fertility setting and no guidance is available yet to inform either clinicians or their patients. This low-risk and low-cost lifestyle choice has the potential to improve fertility without compromising the general wellbeing of the patient. We would like to add a caveat, that a ‘one size fits all’ level of PA cannot be advocated, and a personalised approach, with a holistic take on lifestyle, not just, on smoking and alcohol, but also optimising the appropriate level/types of PA should be recommended to each woman seeking fertility treatment. We already appreciate that PA reduces weight, but in those who do not need to reduce weight, the role of PA in improving their fecundity requires further study. The sole focus on PA for weight loss, rather than the effects of PA on reproductive function itself, has resulted in the current lack of studies comparing types of PA, intensity, and their impact on female fertility. This precludes efficient and effective use of PA as a therapeutic modality in the management of infertility. An adequately powered, optimally designed, clinical trial assessing the role of PA in altering fecundability is urgently needed to evaluate the public health impact of that approach and to gain insights into the biological mechanisms of PA on reproductive function. This is especially pertinent in the era of unknown and unfair funding for fertility treatment across the different regions and countries on a background of intense interest amongst young people on PA and exercise training.

Authorship
Conceptualisation and ethical approval N.T. and D.K.H.; N.T. H.A.L. E.O. and E.S. collected the data, N.T. M.F. V.S. and D.K.H analysed and interpreted the data and wrote the first draft of the manuscript. All authors have read and agreed to the final version of the manuscript.

Acknowledgments
We would like to acknowledge the women who attended the Hewitt Fertility Centre and kindly took time to complete the questionnaire. We would also like to thank Dr Steven Lane for his expert statistical assistance.
Funding

This work was supported by the Wellbeing of Women (grant numbers RTF510 (N.T. and D.K.H.) and RG1073 (D.K.H.) and RG2137 (D.K.H.)). N.T. is supported by an Academic Clinical Lectureship from the National Institute of Health Research. H.A.L. is supported by the Hewitt Fertility Centre/ Liverpool Women’s Hospital NHS Trust.

Conflict of Interest

The authors declare no conflicts of interest.

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NHS. Infertility.


Table 1. Participant demographics. Data are presented as *n (%)* or as mean ± S.D.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, <em>n</em></td>
<td>250</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34 ± 5</td>
</tr>
<tr>
<td>BMI* (kg/m²)</td>
<td>29 ± 7</td>
</tr>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>1 (1 %)</td>
</tr>
<tr>
<td>Normal weight (≥18.5, ≤24.9)</td>
<td>81 (37 %)</td>
</tr>
<tr>
<td>Overweight (≥25, ≤29.9)</td>
<td>54 (24 %)</td>
</tr>
<tr>
<td>Obese Class 1 (≥30, ≤34.9)</td>
<td>47 (21 %)</td>
</tr>
<tr>
<td>Obese Class 2 (≥35, ≤39.9)</td>
<td>19 (9 %)</td>
</tr>
<tr>
<td>Obese Class 3 (≥40)</td>
<td>17 (8 %)</td>
</tr>
<tr>
<td>Smoker*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24 (10 %)</td>
</tr>
<tr>
<td>No</td>
<td>223 (90 %)</td>
</tr>
<tr>
<td>Alcohol Intake*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>145 (59 %)</td>
</tr>
<tr>
<td>No</td>
<td>102 (41 %)</td>
</tr>
<tr>
<td>Regular Periods*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>184 (76 %)</td>
</tr>
<tr>
<td>No</td>
<td>58 (24 %)</td>
</tr>
<tr>
<td>Number of pregnancies*</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>Number of children*</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>Time trying to conceive* (months)</td>
<td>32 ± 24</td>
</tr>
<tr>
<td>Less than 1 year</td>
<td>30 (12 %)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>83 (33 %)</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>77 (31 %)</td>
</tr>
<tr>
<td>Not applicable**</td>
<td>30 (12 %)</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (12 %)</td>
</tr>
<tr>
<td>Previous Fertility treatment</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>180 (92 %)</td>
</tr>
<tr>
<td>IVF</td>
<td>8 (3 %)</td>
</tr>
<tr>
<td>Clomid</td>
<td>11 (4 %)</td>
</tr>
<tr>
<td>IUI</td>
<td>1 (1 %)</td>
</tr>
</tbody>
</table>

BMI (Body Mass Index), IVF (*in vitro* fertilisation), IUI (intra uterine insemination).

* indicates incomplete data set.

**Fertility preservation, Mayer Rokitansky Kuster Hauser (MRKH), on treatment for endometriosis, paralysis, presently single, same sex relationship, male partner known to be infertile.
Table 2 Physical activity levels of the participants ($n = 229$) determined using IPAQ-SF. Data are presented as $n$ (%) or as mean ± S.D.

<table>
<thead>
<tr>
<th>Physical Activity Outcomes</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Activity Level</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>58 (25 %)</td>
</tr>
<tr>
<td>Moderate</td>
<td>105 (46 %)</td>
</tr>
<tr>
<td>Low</td>
<td>66 (29 %)</td>
</tr>
<tr>
<td>Total Physical Activity (min/week)</td>
<td>87 ± 64</td>
</tr>
<tr>
<td>Total Physical Activity (MET-min/week)</td>
<td>1607 ± 1513</td>
</tr>
<tr>
<td>Vigorous Activity (MET-min/week)</td>
<td>427 ± 669</td>
</tr>
<tr>
<td>Moderate Activity (MET-min/week)</td>
<td>278 ± 535</td>
</tr>
<tr>
<td>Walking Activity (MET-min/week)</td>
<td>902 ± 961</td>
</tr>
</tbody>
</table>
Table III. Preferred maximum time of delay to fertility treatment amongst women interested in participating in future research (Respondents, n=73).

<table>
<thead>
<tr>
<th>Delay to fertility treatment</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-month</td>
<td>28 (38)</td>
</tr>
<tr>
<td>3-months</td>
<td>8 (11)</td>
</tr>
<tr>
<td>6-months</td>
<td>6 (8)</td>
</tr>
<tr>
<td>12-months</td>
<td>12 (17)</td>
</tr>
<tr>
<td>Not sure</td>
<td>19 (26)</td>
</tr>
</tbody>
</table>