Evaluation of Chronotype and Sleep Quality in Infertile Population and Comparison With Fertile Population: a Prospective Cohort Study

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Abstract

**Purpose:** Infertility is a stressful condition for couples and can affect patients' circadian rhythm and sleep quality. The goal of this study is to see if there were any differences in chronotype and sleep quality between infertile and fertile people.

**Methods:** A prospective cohort study was conducted in a university hospital-based obstetrics and gynecology clinic. The infertile patient population was a study group and consisted of patients with infertility. Primiparous patients who presented for routine cervical cancer screening follow-up were included in the control group. The Turkish version of the Morningness-Eveningness Questionnaire (MEQ) and Pittsburg Sleep Quality Index (PSQI) scores were evaluated between groups.

**Results:** A total of 227 patients were assessed, and their MEQ and PSQI values compared according to their fertility situation. There were 110 patients in the study (infertile) group and 117 patients in the control (fertile) group. The evening type chronotype proportion (23.6% vs 0.9%, p<0.001) was more common in the infertile group. There was no statistical important difference according to intermediate chronotype proportion between two groups (61.8% vs 59.8%; p=0.35). PSQI > 5 patients were higher in the infertile group proportionally (72.7% vs. 21.4%, p<0.001). The median of MEQ score was significantly higher in the fertile patients (50, IQR=43 – 55 vs. 56, IQR= 51 – 59; p<0.001), and the median of PSQI score was significantly higher in the infertile patients (5, IQR= 4 – 6, vs. 4, IQR= 3 – 5; p<0.001)

**Conclusions:** In the present study we found significantly worse sleep quality, and more evening chronotype in the patients with infertility.

Introduction

Infertility is described as the inability to become pregnant after a year of frequent, unprotected sexual intercourse, and it is becoming more common every year [1]. Quality of life, a complex state, is affected by individual's biological, psychological and social conditions. The relationship between infertility and poor life quality is well known [2]. There are known modifiable risk factors related to poor life quality for infertility, including obesity and smoking. Several determinants, such as physical and psychological status, desire, and partnerships, may have an impact on sexual function.

Additionally, sleep is necessary for vital functions, and sleep characteristics might affect fertility. As a result, there has been a new trend toward evaluating the relationship between sleep quality and fertility. The ideal duration of sleep is defined as 7–9 hours of sleep on a 24-hour time span [3], but in real life, one-third of premenopausal women sleep less than 7 hours [4]. Women not only have shorter sleep durations than men, but they also have higher sleep disruptions, which can be caused by fluctuations in reproductive hormone levels [5].

Sleep falls under the control of endogenous circadian regulation [6]. The secretion of reproductive hormones is also affected by the circadian cycle [6]. Melatonin is the key regulatory hormone in the
control mechanisms, and the suprachiasmatic nucleus is the primary control site on the brain for circadian regulation. These regulatory systems can operate in a variety of ways in different people, resulting in a variety of behavioral phenotypes known as chronotypes. Three sorts of chronotypes are defined as follows: morning-type, intermediate type, and evening type. Morning people are more likely to get up early and stay active during the day. Evening people are the opposites of morning people, while intermediate-type people are those who are neither morning nor evening type. The degree and intensity of a person's cognitive and physical activity throughout the day is influenced by their chronotype.

Several authors investigated the effects of sleep habits and chronotypes on reproductive health. In a systematic review which investigated the impact of sleep on female and male reproductive functions in 2021 [7], they concluded that short sleep duration, evening chronotype, or shift/night work schedules may affect female infertility, male fertility and IVF outcomes. Kloss et al. also showed that sleep disorders or changes in sleep habits directly or indirectly have an impact on reproductive health [8]. Authors suggested three probable theoretic paths between sleep problems and infertility relation: the first one is that hypothalamic-pituitary-adrenal (HPA) axis diseases may cause sleep disturbances. The second one is that sleep disturbances cause HPA change and the last one is that circadian diseases may result in infertility independent of HPA [8].

The association between chronotype and ovarian cycle, menstrual discomfort, menstrual duration, preeclampsia, and premature birth has been studied in several research [9–11]. However, there is a scarcity of data to measure the chronotype and sleep quality of infertile people and prospectively compare them to fertile cohorts. Toffol et al. evaluated 2672 patients retrospectively. Patients with intermediate chronotype had increased risk of infertility when compared to patients with morning chronotype (OR = 1.618, 95% CI = 1.090 to 2.402; p < 0.05) [12]. Moreover, Huang et al., focused on in vitro fertilization (IVF) parameters instead of natural fertility and their results demonstrated that 43.3% of 97 IVF patients had poor sleep quality [13]. On the other hand, Willis et al. did not find any association between shift work and fecundability [14].

We hypothesized that the connection between infertility and sleep quality is a significant clinical issue. The quality of sleep could be a direct or indirect indicator of the reproductive health. There is a scarcity of evidence on the sleep quality of infertile women. As a result, we plan to use standardized questionnaires to evaluate the sleep quality and chronotype of infertile women and compare these parameters to those of fertile women.

**Material And Methods**

Prospective cohort research was done between September 2020 and July 2021 at Bezmialem University Hospital's Department of Obstetrics and Gynecology. The Ethical Committee of Bezmialem University's Medical Faculty accepted the study protocol. All patients signed a written informed consent form. Throughout the investigation, the World Medical Association's Code of Ethics (Declaration of Helsinki) was taken into account.
The research group consisted of women between the ages of 18 and 40 who had been diagnosed with infertility and had failed to conceive after 12 months despite frequent and unprotected sexual intercourse. The women with at least one naturally conceived live birth who administered to the gynecology outpatient clinics for national cervical cancer screening program without any chronic disease nor complaint were included in this study as control group. Patients with a history of mental, neurologic, or sleep disorders, unwillingness to participate, women working night shifts, and patients taking medicines that alter the sleep–wake cycle were all ruled out.

Patients' demographic parameters (age, smoking habits, gravida, parity, infertility length, type of infertility, occupation, and BMI) were gathered, as well as Morningness-Eveningness Questionnaire (MEQ) groups and scores, and Pittsburgh Sleep Quality Index (PSQI) groups and scores. One of the study authors (CO) applied PSQI and MEQ surveys. According to the survey results, sleep quality indices were calculated, and chronotypes were determined.

**Pittsburgh sleep quality index (PSQI)**

The PSQI, which is frequently used to assess sleep quality, has been demonstrated to be beneficial in the study of sleep disorders [15]. In this study, sleep quality was assessed with Pittsburgh Sleep Quality Index (PSQI). It has 19 self-report items composed of seven categories: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. The questions include sleep length, sleep latency, the regularity, and intensity of certain sleeping issues. This index has 24 questions, 19 of which are filled by the individual and five by the individual's spouse or a person with whom they reside. There are seven modules to these 19 scored items: Some are made up of only one object, while others are made up of a number of them. A score of 0–3 is assigned to each module. These seven component ratings yield a total index score ranging from 0 to 21. Scores <5 were evaluated as good sleep quality, and scores >5 were set as poor sleep quality.

**Morningness–eveningness questionnaire (MEQ)**

The MEQ scale is used to assess a person's chronotype [16]. We assessed chronotypes of patients with Morningness-Eveningness Questionnaire (MEQ). The questionnaire has 19 questions concerning an individual's physical and psychological performance throughout a 24-hour period, as well as their favorite periods for various activities. Scores range from 16 to 86, with scores between 16 and 41 indicating evening type, 42–58 indicating intermediate type, and 59–86 indicating morning type.

**Statistical analyses**

Data analyses were performed using SPSS Version 21.0 (IBM Corporation, Armonk, NYC, USA). Samples were tested with the Kolmogorov Smirnov test to determine the normality of distributions. According to the results, non-parametric tests were preferred. Continuous variables were compared with Mann–Whitney U test. Categorical variables were compared with Fisher's exact test. A P value of < 0.05 was considered statistically significant. After calculating sample size and power, it was concluded that 103
patients in each group were sufficient (power of 0.80, 0.05, and =0.20). Changes in the PSQI were used to calculate the power [17]. Each group consisted of at least 103 patients.

**Results**

A total of 227 patients were included in the study. There were 110 patients in the study (infertile) group and 117 patients in the control (fertile) group. Table 1 summarizes the demographic and clinical features of the patients. The research and control groups had mean ages of 32 (24–36) and 32 (29–36), respectively. There are no statistically significant differences between groups in terms of age, BMI, smoking, and profession (Table 1). Parity and gravida were significantly different between fertile and infertile groups (Table 1). The median of duration of infertility in the study group was 4 (3–7) and 68.2% of the study group is primary infertility and 31.8% of the study group is secondary infertility. Grouping participants compared MEQ and PSQI values according to fertility situations. An overview of our findings is presented below; PSQI and MEQ scores of the patients are shown in Table 2.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Infertile Group (n = 110)</th>
<th>Fertile (Control) Group (n = 117)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>32 (24–36)</td>
<td>32 (29–36)</td>
<td>NS</td>
</tr>
<tr>
<td>Gravida, median (IQR)</td>
<td>0 (0–1)</td>
<td>2 (1–2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Parity, median (IQR)</td>
<td>0 (0–0)</td>
<td>2 (1–2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$), median (IQR)</td>
<td>25 (22–28)</td>
<td>24 (22–28)</td>
<td>NS</td>
</tr>
<tr>
<td>Infertility time (years), median (IQR)</td>
<td>4 (3–7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infertility type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary infertility, n (%)</td>
<td>75 (68.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary infertility, n (%)</td>
<td>35 (31.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>22 (20%)</td>
<td>26 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>Non-smokers, n (%)</td>
<td>88 (80%)</td>
<td>91 (77.8%)</td>
<td></td>
</tr>
<tr>
<td>Profession</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Housewife, n (%)</td>
<td>47 (42.7%)</td>
<td>45 (38.5%)</td>
<td></td>
</tr>
<tr>
<td>Officer, n (%)</td>
<td>61 (55.5%)</td>
<td>72 (61.5%)</td>
<td></td>
</tr>
<tr>
<td>Shift Worker, n (%)</td>
<td>2 (1.8%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

NS: Not significant, p > 0.05

IQR: Interquartile range

Values are reported as median (IQR), number (percentage)
Table 2
Comparison of MEQ and PSQI scores of groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Infertile Group (n = 110)</th>
<th>Fertile (Control) Group (n = 117)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEQ Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morningness, n (%)</td>
<td>16 (14.5%)</td>
<td>46 (39.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intermediate, n (%)</td>
<td>68 (61.8%)</td>
<td>70 (59.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Eveningness, n (%)</td>
<td>26 (23.6%)</td>
<td>1 (0.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MEQ Score, median (IQR)</td>
<td>50 (43–55)</td>
<td>56 (51–59)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PSQI Group</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&lt;5, n (%)</td>
<td>30 (27.3%)</td>
<td>92 (78.6%)</td>
<td></td>
</tr>
<tr>
<td>&gt;5, n (%)</td>
<td>80 (72.7%)</td>
<td>25 (21.45%)</td>
<td></td>
</tr>
<tr>
<td>PSQI Score, median (IQR)</td>
<td>5 (4–6)</td>
<td>4 (3–4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NS: Not significant, p &gt; 0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQR: Interquantile range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Values are reported as median (IQR), number (percentage)</td>
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</tbody>
</table>

The median of MEQ scores in study and control groups was 50 (43–55) vs. 56 (51–59); respectively. It was significantly higher in the fertile group (p < 0.001). There was a significant difference between infertile and fertile groups in terms of chronotype. The proportion of patients in study and control groups were 14.5% vs 38.3% of morning type (p < 0.001); 23.6% vs 0.9% of evening type (p < 0.001) and 61.8% vs. 59.8% of intermediate type (p = 0.35), respectively. The proportion of evening type chronotype was more and the proportion of morning type chronotype was lesser in the infertile group when compared to the fertile population. There was no statistically important difference between the two groups’ intermediate chronotype proportion.

The median PSQI scores were 5 (1–12) and 4(1–9) in the study and control groups, respectively. The median of PSQI score was significantly higher in the infertility group (5, IQR = 4–6, vs. 4, IQR = 3–5; p < 0.001) (Table 2). PSQI > 5 patients (poor sleep quality) were higher in the infertile group proportionally (72.7% vs. 21.4%, p < 0.001) (Table 2).

**Discussion**

To the best of the authors' knowledge, this is the first study to look at the quality of sleep in infertile women and compare the results to those of fertile women. Our findings revealed that the morning chronotype was proportionately more prevalent in the fertile group and the evening chronotype was more
frequent in the infertile group. When compared to fertile women, our results show that infertile women have low sleep quality and high PSQI scores.

Short sleep duration, inadequate sleep, and poor sleep quality were shown to be connected with evening chronotype, and insufficient sleep was found to reduce the ability to cope with unpleasant emotions. Our results might reflect the relationship between chronotype, sleep quality and the ovarian cycle. The reproduction cascade starts with ovulation and everything affecting the ovulation can also affect the fertility status of a person. Kang et al. and Xing et al. reported more menstrual irregularities in women with insomnia or poor sleep quality [18, 19]. In addition, Toffol et al. reported an association between intermediate chronotype and higher risk of infertility than morning chronotype (OR 1.62, 95% CI 1.09–2.40; p < 0.05)(12). Similarly, we also found morning chronotype patients less in the infertile group; on the contrary, we found significantly higher evening chronotype patients in the infertile group. This difference might have originated from differences within study cohorts. Toffol et al. conducted a study on the Finnish population, and the mean age of the cohort was 54; in contrast, our study was conducted on the Turkish population with a mean age of 32. Furthermore, Willis et al. reported no significant association between sleep duration and fecundability and no significant association between work schedules and fecundability [14]. However, we found evening chronotype more in the infertile group. They did not use a MEQ questionnaire for the determination of chronotypes; the shift work status determined groups. Study was performed with 6,873 American participants from couples attempting pregnancy more than 6 months. Moreover, their time criterion was six months for fecundability; our time criterion for infertility was one year.

Consequently, all of these differences between populations and methods might be the reason for the conflicting results. Lastly, Goksu et al., a group of investigators from Turkey investigated the improvement of the PSQI scores in grade 4 endometriosis patients after surgery, and they found that the proportion of those with bad sleep quality was more in the infertile population [20]. That was similar to our results. Taken together, our findings and the findings of previous studies point towards there being differences in terms of sleep quality and chronotype status between fertile and infertile patients. This should not be forgotten in the assessment of infertile women.

The main strength of this study is, that to our knowledge, our study was the first study to investigate the sleep quality and chronotype differences prospectively between fertile and infertile populations. There were also limitations of our study. Even though we included a statistically adequate number of patients, our sample size was less than that of other research that looked into sleep quality and its impact on natural fertility, but those studies were retrospective. Because of the time limit of prospective studies, it would be hard to collect a similar number of patients with identical retrospective studies. However, the sample size was calculated with the power of 0.80, and the study was completed with a fair number of patients.

In conclusion, in the present article, we concluded infertile patients had a worse sleep quality, and evening chronotype was significantly more common in the infertile group. According to our findings, there is a
possible link between all illnesses and infertility. Future studies may extend findings of this work with larger cohorts. Also, sleep quality and chronotype should be taken into account for infertility management. It may possibly be a candidate for modifiable life factors in infertility management.

Declarations

Declaration of interest:

None.

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Author Contribution:

Özçelik C: Project development, Data collection
Varlı B: Data analysis, Manuscript editing
Gökçe A: Data analysis, Manuscript writing
Takmaz T: Project development, Data collection
Çetin Ç: Project development, Data collection
Ozcan P: Project development, Data collection, Manuscript writing

Conflict of Interest:

The authors declare that they have no conflict of interest.

References


